# NHEERL HUMAN RESEARCH SIGN-OFF SHEET

**PI *(Name/Division)*:** Danelle T. Lobdell/ EPHD

**PROTOCOL TITLE:** An epidemiologic health study of manganese (Mn) exposure in East Liverpool, Ohio

**NAME OF APPROVING IRB:** San Francisco State University/ agreement with UNC Chapel Hill

**IRB-ASSIGNED PROTOCOL NUMBER:** H11-39

| **REVIEWS *(Attach to EPA Protocol Package)*** | | |
|---|---|---|
| **Reviewer** | **Signature** | ***Date*** |
| *Peer Reviewer1 (printed or typed)* | | |
| Peer Reviewer2 *(printed or typed)* | | |
| Statistician | | |
| Physician | | |
| Other | | |
| **APPROVALS** | | |
| **Official** | **Signature** | **Date** |
| Branch Chief - Tim Wade | | |
| IRB | *(Attach signed approval letter)* | |
| Dosing Review Officer (if applicable) | | |
| Division Quality Assurance Officer | | |
| HRPO Director | | |
| Division Director | | |
| Associate Director for Health | *(Indicated by approval letter)* | |
| Agency Human Subjects Research Review Official | *(Indicated by approval letter)* | |

revised 5/15/2008

**MEMORANDUM**

**Date:** August 10, 2011

**Subject:** Request for protocol review

**From:** Danelle Lobdell, EPHD/EB

**To:** Julian Preston, NHEERL Associate Laboratory Director for Health

Enclosed, please find the Protocol Package for "An epidemiologic health study of manganese (Mn) exposure in East Liverpool, Ohio." Potential neurotoxicity from airborne Mn exposure has been a community and risk assessment concern for more than a decade in Region 5. This study will evaluate whether long term (minimum 10 years) residential airborne Mn exposure can affect human health. This Regional Applied Research Effort (RARE) project is a joint effort between Region 5 and Dr. Danelle Lobdell representing ORD, that will examine neurotoxic effects of Mn within three communities - high level air exposure community, mid to low range air exposure community, and no air exposure community. This study will utilize data already collected in two Ohio communities and add a third, highly exposed community. East Liverpool residents have probably been exposed to some of the highest long term outdoor air Mn concentrations in the US. Health data from this community could advance knowledge of potential effects of residential airborne Mn exposure (an issue of global, national and R5 interest) and can help evaluate the need for further pollution controls.

Included in this package are:
NHEERL Human research sign-off sheet
NHEERL Fact Sheet
NHEERL Study Justification Document
IRB approval letter
IRB application
IRB approved research protocol
Ethics training report

August, 2011

**NHEERL Fact Sheet**

DRAFT: For Internal Agency Use Only

# An epidemiologic health study of manganese (Mn) exposure in East Liverpool, Ohio

**Impact Statement:** This study will address research questions under Sustainable and Healthy Communities (under Theme 2, Project 11 Additional Technical Support to Program Offices and Regions) and Air, Climate, and Energy Research Programs (under Regional Technical Support). This Regional Applied Research Effort project is a joint effort between Region 5 and ORD Scientists that will examine neurotoxic effects of Mn within three communities, high level air exposure community, mid to low range air exposure community, and no air exposure community. This work is important in that either positive results (differences between East Liverpool and comparison communities) or negative results (little or no differences among communities) inform the issue of potential health effects of residential airborne Mn exposure, a recognized gap in Mn health effects literature. Both outcomes can also help inform the need for greater airborne Mn control. In addition, the present proposal addresses the USEPA Administrator's environmental justice priority: the poverty rate is higher in East Liverpool (25.2%) than in Marietta (16.9%), Mt. Vernon (15.6%), Ohio (7.8%) or the U.S. (9.2%). East Liverpool residents have probably been exposed to some of the highest long term outdoor air Mn concentrations in the US. Health data from this community could advance knowledge of potential effects of residential airborne Mn exposure (an issue of global, national and R5 interest) and can help evaluate the need for further pollution controls. This information would also add context to the USEPA School Air Toxics study that includes schools in both Marietta and East Liverpool.

**Background:**

This project is a Regional Applied Research Effort (RARE) in Region 5. Potential neurotoxicity from airborne Mn exposure has been a community and risk assessment concern for more than a decade in Region 5 (e.g. OH, MI). The RARE program funded a 2009-2010 Mn health study in Marietta OH near a large industrial emitter of airborne Mn, led by Rosemarie Bowler of San Francisco State University. Mt. Vernon OH, demographically similar to Marietta but without large industrial Mn emission sources, was used as the comparison community for Marietta. Initial Marietta-Mt. Vernon comparisons generally indicate a lack of major health effect differences between the two towns. Whether this extends to East Liverpool OH, an area of much higher (up to 50-fold) outdoor air Mn concentrations is the present research question of interest, and a central reason for extending the Marietta-Mt. Vernon study.

**Study Description:**

This study will evaluate whether long term (minimum 10 years) residential airborne Mn exposure can affect human health. Participants in East Liverpool will be randomly selected within a 2.5-mile radius of the exposure source (a Mn warehousing and packaging facility) and appropriate exclusion criteria will be applied. Following consent procedures, participants will be administered a battery of tests of cognitive function and motor efficiency. A brief neurological examination will be conducted using the Unified Parkinson's Disease Rating Scale (UPDRS). The Computerized Adaptive Testing System (CATSYS) will be used to assess postural sway and hand tremor. Whole blood will be analyzed for Mn, cadmium (Cd), mercury (Hg), and lead (Pb). Serum will be analyzed for ferritin and two liver enzymes. Hair samples and toenail clippings will be analyzed for Mn levels. Additionally, participants will be asked to complete questionnaires asking about their demographic information, mood, diet, occupational history, behavioral habits, and health history. Data collected from East Liverpool participants will be compared with previously collected data from the demographically similar, but less Mn-exposed town of Marietta, Ohio and the comparison town of Mount Vernon, Ohio where air Mn exposure is not of concern.

**Timeline:**

Projected starting date: 7/2011; Projected closing date: 8/2014
IRB status: approved 8/ /2011; EPA review status: pending

**Contact:** Danelle T. Lobdell, Ph.D., Environmental Public Health Division, lobdell.danelle@epa.gov, (919)843-4434

August, 2011

**Study Justification document**

An epidemiologic health study of manganese (Mn) exposure in East Liverpool, Ohio

**Principal Investigator:** Danelle Lobdell, US EPA ORD/NHEERL/EPHD
Co-Investigators: George Bollweg, US EPA Region 5
Contracted to Rosemarie Bowler, San Francisco State University

**Relevance of the research to agency's mission:**

This study will address research questions under Sustainable and Healthy Communities (under Theme 2, Project 11 Additional Technical Support to Program Offices and Regions) and Air, Climate, and Energy Research Programs (under Regional Technical Support). This Regional Applied Research Effort project is a joint effort between Region 5 and ORD Scientists that will examine neurotoxic effects of Mn within three communities, high level air exposure community, mid to low range air exposure community, and no air exposure community. Health data from this community could advance knowledge of potential effects of residential airborne Mn exposure (an issue of global, national and R5 interest) and can help evaluate the need for further pollution controls.

**Value added by human studies**

Through another RARE funded study, in 2009-2010 data was collected examining Mn and health outcomes in Marietta OH where the there is a large industrial emitter of airborne Mn. Mt. Vernon OH, demographically similar to Marietta but without large industrial Mn emission sources, was used as the comparison community for Marietta. Initial Marietta-Mt. Vernon comparisons generally indicate a lack of major health effect differences between the two towns. Whether this extends to East Liverpool OH, an area of much higher (up to 50-fold) outdoor air Mn concentrations is the present research question of interest, and a central reason for extending the Marietta-Mt. Vernon study. There are very few studies examining air Mn exposure in the general population. Most studies focus on high occupational exposures. The value added for this study is to examine health outcomes (primarily neurological effects) among a community exposed to high levels of Mn from an air source.

**Value to society of public health benefits**

Some of the highest chronic US residential Mn inhalation exposure is likely to have occurred in East Liverpool. The proposed work is important in that either positive results (differences between East Liverpool and comparison communities) or negative results (little or no differences among communities) inform the issue of potential health effects of residential airborne Mn exposure, a recognized gap in Mn health effects literature. Both outcomes can also help inform the need for greater airborne Mn control. The study will address concerns about the potential health effects of Mn exposure by assessing the health status of a representative sample of East Liverpool residents. The study will provide important information about potential effects of gradients of exposure to Mn from industrial sources in non-occupational environmental settings. Furthermore, the study will add to the limited literature on the relationship between various biomarkers of Mn (blood, toenails, hair).

**Value to decision making processes by the scientific merit**

East Liverpool residents have probably been exposed to some of the highest long term outdoor air Mn concentrations in the US. Health data from this community could advance knowledge of potential effects of residential airborne Mn exposure (an issue of global, national and R5 interest)

and can help evaluate the need for further pollution controls. This information would also add context to the USEPA School Air Toxics study that includes schools in both Marietta and East Liverpool. In addition, the present proposal addresses the USEPA Administrator's environmental justice priority: the poverty rate is higher in East Liverpool (25.2%) than in Marietta (16.9%), Mt. Vernon (15.6%), Ohio (7.8%) or the U.S. (9.2%).

**Subject safety**

- To ensure privacy, all neuropsychological testing will be conducted in a private room with only the participant and examiner present. Collection of blood, toenail, and hair samples will also take place in a separate, private room, as will the CATSYS and UPDRS examinations. The P.I. will conduct a brief interview with each participant in a secluded area. No phone conversations with participants will be conducted in public – all phone conversations will take place in private office settings.
- Drawing venous blood from the arm may cause minimal pain when the needle is inserted. There is also a slight risk of bruising and infection where the needle punctures the skin. In rare cases, some people may experience lightheadedness, nausea, or fainting. The certified phlebotomist is trained in recognizing and dealing with these types of reactions. All possible accommodations will be made should this occur. Cutting a small amount of hair will be done with a blunted scissors which will prevent any accidental injuries. Blood samples will also be marked with an ID number only to ensure those analyzing the blood/serum are blinded to the identity of the participant. Arrangements will be made with a local physician on call, who will be recruited by a local colleague practicing in East Liverpool. The pager number and location of this local physician will be obtained so he/she may be contacted and available to address any medical emergency that may arise. Although such emergencies are highly unlikely, a participant, if necessary can be brought to the nearest Emergency Room at the local hospital.
- There is a risk of experiencing slight fatigue during testing. Testers are trained to look for signs of fatigue and a break will promptly be offered. The participants will also be informed that they can take a break or discontinue testing at any point.

**NHEERL ethics requirements**

Only the project principle investigator (Rosemarie Bowler, San Francisco State University) will have access to names and IDs. US EPA will obtain the data with ID numbers only at the end of the contract year. Dr. Lobdell is in compliance with NHEERL ethics requirements and have taken the UNC CITI ethics training. Dr. George Bollweg will not have access to the data.

**Communication strategy**

Region 5 will be the primary communication source for US EPA for this study. A community meeting will be held within one year of data collection to provide overall study results. Also, all participants will receive individual study results.

**Reviews of Protocol**

This study protocol is almost exactly the same (only difference is adding in hair and toe nail samples of Mn) as was conducted in Marietta and Mt. Vernon, OH which was funded through a cooperative agreement which the protocol was reviewed extensively through this process (three

external reviewers and one internal EPA reviewer). Also, this study proposal was approved through the RARE process which was reviewed extensively throughout the Agency.

**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**
NATIONAL HEALTH & ENVIRONMENTAL EFFECTS RESEARCH LABORATORY
OFFICE OF RESEARCH AND DEVELOPMENT
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Phone: 919-843-4434, Fax: 919-966-7584
Email: lobdell.danell@epa.gov

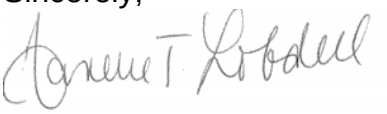
August 4, 2011

To Whom It May Concern:

Enclosed, please find Application for IRB Approval for the following study "An Epidemiologic Health Study of Manganese Exposure in Adult Residents of East Liverpool, Ohio." After discussions with Diane in your office, I would like to provide some context for this study. This is a U.S. Environmental Protection Agency Funded study to San Francisco State University (SFSU). The funded PI on the study is Dr. Rosemarie Bowler. We are submitting this protocol through the UNC IRB because our Human Subjects Review Official does have oversight on this project because the funding mechanism is contract. However, this study is an expansion of a previously completed study by Dr. Bowler's team which was funded as a grant and thus did not have direct oversight from our Human Subjects Review Official. Diane advised me to complete the application as the technical expert of the funder and include the already approved protocol from San Francisco State University IRB and to notify you that the Office for the Protection of Human Subjects at San Francisco State University will be the primary IRB of record for this field study.

Please note that a few of the documents have had small minor edits since the approval from SFSU. Dr. Bowler will submit amendments to SFSU's Office for the Protection of Human Subjects for all documents that have had edits after your review. These documents include: consent form, phone recruitment script, sample feedback letter and the study protocol. Please do not hesitate to contact me if you should have any questions.

Sincerely,



Danelle T. Lobdell, Ph.D.

OFFICE OF HUMAN RESEARCH ETHICS -- Institutional Review Board

# INSTRUCTIONS FOR APPLICATION FOR IRB APPROVAL OF HUMAN SUBJECTS RESEARCH

*Version June 25, 2009*

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## What is the purpose of this form?

This application is to seek *initial* IRB approval for a research study.

## What parts of this application should you submit?

Answer all questions, or mark "not applicable," when appropriate. Do not alter wording or delete questions from this form.

- For ***all studies***, submit Part A, which consists of these sections:
  - Part A.1. Contact Information, Agreements, and Signatures
  - Part A.2. Summary Checklist
  - Part A.3. Conflict of Interest Questions and Certification
  - Part A.4. Questions Common to All Studies
  - Part A.5. The Consent Process and Consent Documentation (including Waivers)

- For ***studies that involve direct interaction*** with human subjects (any contact with subjects including questionnaires, interviews, focus groups, observation, treatment interventions, etc), submit:
  - Part B. Questions for Studies that Involve Direct Interaction with Human Subjects

- For ***studies*** that use existing data, records or human biological specimens, including for use in identifying potential subjects, submit:
  - Part C. Questions for Studies using Existing Data, Records or Human Biological Specimens

**Note**: You should submit Parts B or C only as applicable. If the study involves *both* direct interaction *and* use of existing materials, use both Parts B and C in addition to Part A.

## Who can serve as principal investigator (PI)?

The PI is the person who will personally conduct or supervise this research study. Under most circumstances, this will be a faculty member. For IRB communication purposes, a trainee/student may be listed as PI. However, a faculty advisor must be identified, who holds ultimate responsibility for ensuring that this project complies with all University, regulatory, and fiscal requirements.

→ *See next page for additional instructions*

**---- Instructions – Do not submit this page with your application ----**

Complete submission instructions can be found at http://ohre.unc.edu/submission_instructions.php. **All application and consent materials must be copied or printed on one side only**. See the checklist on page 1 of the application itself for items to include and number of copies.

Some applications require additional review prior to the IRB submission. Examples include the Clinical and Translational Research Center (formerly the GCRC and CCCT facilities) http://tracs.unc.edu/index.php?option=com_content&view=article&id=285&Itemid=312) or the Oncology Protocol Review Committee (PRC; http://cancer.med.unc.edu/research/prc/default.asp). See their web sites for details.

Many schools, departments, centers and institutes in Academic Affairs have local review committees that review before the IRB. See http://ohre.unc.edu/submission_instructions.php for a list of these units or consult your own unit for details.

**Address for all Applications and Other Correspondence**

IRB
CB# 7097, Medical Building 52
105 Mason Farm Road
Chapel Hill, NC 27599-7097

**Types of Review**

There are three levels of IRB Review (full board, expedited, and exempt), determined by the nature of the project, level of potential risk to human subjects, and the subject population. *The type of review applicable to a particular study is determined by the IRB.* Regardless of the kind of review, all applications use the same submission form.

Exempt and expedited review can be given to studies that constitute no more than minimal risk to the human subjects, i.e., the risk one experiences in daily living. These reviews are done in the IRB office on a continual basis.

Full board review is required for studies that involve greater than minimal risk or vulnerable populations that require special protection by the IRB. These require review by the convened IRB. See http://ohre.unc.edu/guide_to_irb.php for additional guidance.

**---- Instructions – Do not submit this page with your application ----**

OFFICE OF HUMAN RESEARCH ETHICS
Institutional Review Board

APPLICATION FOR IRB APPROVAL OF
HUMAN SUBJECTS RESEARCH
*Version June 25, 2009*

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## Part A.1. Contact Information, Agreements, and Signatures

**Date:** August 1, 2011

**Title of Study:** An Epidemiologic Health Study of Manganese Exposure in adult residents of East Liverpool, Ohio

**Name and degrees of Principal Investigator**: Dr. Rosemarie M. Bowler, Ph.D., M.P.H.
Department: Psychology, San Francisco State University Mailing address/CB #:
8371 Kent Dr., El Cerrito, CA 94530
UNC-CH PID: Pager:
Phone #: 510-236-5599 Fax #: 510-236-3370 Email Address: rbowl@sfsu.edu

**For trainee-led projects:** __ graduate __ postdoc __ resident __ other
**Name of faculty advisor**:
Department: Mailing address/CB #:
Phone #: Fax #: Email Address:

**Center, institute, or department in which research is based if other than department(s) listed above:**

**Name of Project Manager or Study Coordinator (if any):**

List **all other project personnel** including co-investigators, and anyone else who has contact with subjects or identifiable data from subjects. **Include name, location (UNC or specific outside location), role and email address for each person who should receive electronic copies of IRB correspondence to PI.**

**Collaborators**

**Examiners/Psychometricians**

**Name of funding source or sponsor (*please do not abbreviate*)**: United States Environmental Protection Agency
__ not funded X Federal __ State __ industry __ foundation __ UNC-CH
__ other (specify):

**For external funding, RAMSeS proposal number** (from Office of Sponsored Research): N/A

**For industry sponsored research (if applicable):**

Sponsor's master protocol version #: Version date:

Investigator Brochure version #: Version date:

Any other details you need documented on IRB approval:

## Checklist of Items to Include with Your Submission

**Include the following items with your submission**, where applicable.

- Check the relevant items below and include one copy of all checked items 1-11 in the order listed.
- Also include two additional collated sets of copies (sorted in the order listed) for items 1-6.

**Applications must "stand alone" and should provide all information requested, i.e., complete answers must be contained in the application. While you may reference other documents with supporting information, do not respond solely by stating "see attached."**

**Applications will be returned if these instructions are not followed.**

| Check | Item | Total No. of Copies |
|---|---|---|
| □ | 1. This application. One copy must have original PI signatures. | 3 |
| □ | 2. Consent and assent forms (include DHHS-approved sample, when one exists), fact or information sheets, phone and verbal consent scripts. | 3 |
| □ | 3. HIPAA authorization addendum to consent form. | 3 |
| □ | 4. All recruitment materials including final copies of printed advertisements, audio/video taped advertisements, scripts, flyers, letters, and emails. | 3 |
| □ | 5. Questionnaires, focus group guides, scripts used to guide phone or in-person interviews, etc. | 3 |
| □ | 6. Documentation of reviews from any other committees (e.g., Clinical and Translational Research Center (CTRC), Oncology Protocol Review Committee, or local review committees in Academic Affairs). | 3 |
| □ | 7. Protocol, grant application or proposal supporting this submission, if any (e.g., extramural grant application to NIH or foundation, industry protocol, student proposal). If there is a cover sheet for the grant proposal it is to be included. These must be submitted if an external funding source or sponsor is checked on the previous page. | 1 |
| □ | 8. Addendum for Multi-Site Studies where UNC-CH is the Lead Coordinating Center. | 1 |
| □ | 9. Data use agreements (may be required for use of existing data from third parties). | 1 |
| □ | 10. Only for those study personnel *not* in the online UNC-CH human research ethics training database (http://cfx3.research.unc.edu/training_comp/): Documentation of required training in human research ethics. | 1 |
| □ | 11. For drug studies, Investigator Brochure if one exists. If none, include package insert for previously approved uses.. | 1 |

**Principal Investigator**: I will personally conduct or supervise this research study. I will ensure that this study is performed in compliance with all applicable laws, regulations and University policies regarding human subjects research. I will obtain IRB approval before making any changes or additions to the project. I will notify the IRB of any other changes in the information provided in this application. I will provide progress reports to the IRB at least annually, or as requested. I will report promptly to the IRB all unanticipated problems or serious adverse events involving risk to human subjects. I will follow the IRB approved consent process for all subjects. I will ensure that all collaborators, students and employees assisting in this research study are informed about these obligations. All information given in this form is accurate and complete.

Signature of Principal Investigator _____ Date _____

Note: The following signature is not required for applications with a student PI.

**Department or Division Chair, Center Director (or counterpart) of PI:** (or Vice-Chair or Chair's designee if Chair is investigator or otherwise unable to review): I certify that this research is appropriate for this Principal Investigator, that the investigators are qualified to conduct the research, and that there are adequate resources (including financial, support and facilities) available. If my unit has a local review committee for pre-IRB review, this requirement has been satisfied. I support this application, and hereby submit it for further review.

Signature of Department Chair or designee _____ Date _____

Print Name of Department Chair or designee _____ Department _____

| Part A.2. Summary Checklist *Are the following involved?* | Yes | No |
|---|---|---|
| A.2.1. Existing data, research records, patient records, and/or human biological specimens? | x | __ |
| A.2.2. Surveys, questionnaires, interviews, or focus groups with subjects? | x | __ |
| A.2.3. Videotaping, audiotaping, filming of subjects, or analysis of existing tapes? | __ | x |
| A.2.4. Do you have specific plans to enroll subjects from these vulnerable or select populations: | | |
| a. UNC-CH students or UNC-CH employees? | __ | x |
| b. Non-English-speaking? | __ | x |
| c. Decisionally impaired? | __ | x |
| d. Patients? | __ | x |
| e. Prisoners, others involuntarily detained or incarcerated, or parolees? | __ | x |
| f. Pregnant women? | __ | x |
| g. Minors (less than 18 years)? ***If yes***, give age range: to years | __ | x_ |
| A.2.5. a. Are sites outside UNC-CH engaged in the research? | x | __ |
| b. Is UNC-CH the sponsor or lead coordinating center for a multi-site study? | __ | x |
| ***If yes,*** include the ***Addendum for Multi-site Studies***. | | |
| ***If yes***, will any of these sites be outside the United States? | __ | __ |
| ***If yes***, is there a local ethics review committee agency with jurisdiction? (provide contact information) | __ | __ |
| A.2.6. Will this study use a data and safety monitoring board or committee? | __ | x |
| ***If yes:*** UNC-CH NC TraCS DSMB? (must apply separately) | __ | __ |
| Lineberger Cancer Center DSMC? | __ | __ |
| Other? Specify: | __ | __ |
| A.2.7. a. Are you collecting sensitive information such as sexual behavior, HIV status, recreational drug use, illegal behaviors, child/physical abuse, immigration status, etc? | __ | x |
| b. Do you plan to obtain a federal Certificate of Confidentiality for this study? | __ | __ |
| c. Is this research classified (e.g., requires security clearance)? | __ | __ |
| A.2.8. a. Investigational drugs? (provide **IND #** ) | __ | x |
| b. Approved drugs for "non-FDA-approved" conditions? | __ | __ |
| *All studies testing substances in humans must provide a letter of acknowledgement from the UNC Health Care Investigational Drug Service (IDS).* | | |
| A.2.9. Placebo(s)? | __ | x |
| A.2.10. Investigational devices, instruments, machines, software? (provide **IDE #** ) | __ | x |
| A.2.11. Fetal tissue? | __ | x |
| A.2.12. Genetic studies on subjects' specimens? | __ | x |
| A.2.13. Storage of subjects' specimens for future research? | x | __ |
| ***If yes**, see instructions for **Consent for Stored Samples**.* | | |
| A.2.14. Diagnostic or therapeutic ionizing radiation, or radioactive isotopes, which subjects would not receive otherwise? | __ | x |
| ***If yes**, approval by the **UNC-CH Radiation Safety** **Committee** is required.* | | |
| A.2.15. Recombinant DNA or gene transfer to human subjects? | __ | x |
| ***If yes**, approval by the **UNC-CH Institutional Biosafety** **Committee** is required.* | | |
| A.2.16. Does this study involve UNC-CH cancer patients? | __ | x |
| ***If yes**, submit this application directly to the **Oncology Protocol Review Committee**.* | | |
| A.2.17. Will subjects be studied in the Clinical and Translational Research Center (CTRC) or is the CTRC involved in any other way with this study? If yes, obtain the ***CTRC Addendum*** *and submit completed application (IRB application and Addendum) directly to the CTRC. The CTRC includes facilities located on the 3rd floor of the Main Hospital (formerly GCRC) and Ground floor Burnett-Womack (formerly CCCT).* | __ | x |
| A.2.18. Will gadolinium be administered as a contrast agent? | ..__ | ..x |
| A.2.19. Will subjects' Social Security Number (SSN) be collected for: | | |
| a. processing payments greater than $200 per year, to support IRS reporting (see also B.6)? | __ | x |
| b. processing payments of any amount through UNC-CH Accounts Payable? | __ | x |
| c. use as a unique identifier for study tracking purposes for national registry or database? | __ | x__ |

| | | |
|---|---|---|

## Part A.3. Conflict of Interest Questions and Certification

The following questions apply to **all investigators and study staff** engaged in the design, conduct, or reporting results of this project **and/or their immediate family members.** For these purposes, "family" includes the individual's spouse and dependent children. "Spouse" includes a person with whom one lives together in the same residence and with whom one shares responsibility for each other's welfare and shares financial obligations.

| | | |
|---|---|---|
| A.3.1. Currently or during the term of this research study, does any member of the research team or his/her family member have or expect to have: | | |
| (a) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with the sponsor of this study? | __ yes | _X_ no |
| (b) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with an entity that owns or has the right to commercialize a product, process or technology studied in this project? | __ yes | _X_ no |
| (c) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with an entity engaged in the performance of this project as a subcontractor, sub-recipient or vendor? | __ yes | _X_ no |
| (d) A board membership of any kind or an executive position (paid or unpaid) with the sponsor of this study or with an entity that owns or has the right to commercialize a product, process or technology studied in this project? | __ yes | _X_ no |
| A.3.2. Has the University or has a University-related foundation received a cash or in-kind gift from the sponsor of this study for the use or benefit of any member of the research team? | __ yes | _X_ no |
| A.3.3. Has the University or has a University-related foundation received a cash or in-kind gift for the use or benefit of any member of the research team from an entity that owns or has the right to commercialize a product, process or technology studied in this project? | __ yes | _X_ no |

**If the answer to ANY of the questions above is *yes***, the affected research team member(s) must complete and submit the form, which is accessible online at http://coi.unc.edu. List name(s) of all research team members for whom any answer to the questions above is *yes*:

_____

**<u>Certification by Principal Investigator</u>: By submitting this IRB application, I (the PI) certify that the information provided above is true and accurate regarding my own circumstances, that I have inquired of every UNC-Chapel Hill employee or trainee who will be engaged in the design, conduct or reporting of results of this project as to the questions set out above, and that I have instructed any such person who has answered "yes" to any of these questions to complete and submit for approval a Conflict of Interest Evaluation Form. I understand that as Principal Investigator I am obligated to ensure that any potential conflicts of interest that exist in relation to my study are reported as required by University policy.**

_____ _____

Signature of Principal Investigator Date

## Part A.4. Questions Common to All Studies

*For all questions, if the study involves only secondary data analysis, focus on your proposed design, methods and procedures, and not those of the original study that produced the data you plan to use.*

*Complete answers must be provided. While you may reference other documents with supporting information, do not respond solely by stating "see attached."*

A.4.1. **Brief Summary**. Provide a *brief* non-technical description of the study, which will be used in IRB documentation as a description of the study. Typical summaries are 50-100 words. *Please reply to each item below, retaining the subheading labels already in place, so that reviewers can readily identify the content.*

Purpose: The purpose of this study is to assess if there are health effects associated with exposure to manganese (Mn) in air in adult residents of a Mn-exposed community.

Participants: 100 randomly selected long-term residents (≥10 years) of East Liverpool, Ohio between the ages of 30 to 75 years

Procedures (methods): Participants will be randomly selected within a 2.5-mile radius of the exposure source (a Mn warehousing and packaging facility) and appropriate exclusion criteria will be applied (see proposal). Following consent procedures, participants will be administered a battery of tests of cognitive function and motor efficiency. A brief neurological examination will be conducted using the Unified Parkinson's Disease Rating Scale (UPDRS). The Computerized Adaptive Testing System (CATSYS) will be used to assess postural sway and hand tremor. Whole blood will be analyzed for Mn, cadmium (Cd), mercury (Hg), and lead (Pb). Serum will be analyzed for ferritin and two liver enzymes. Hair samples and toenail clippings will be analyzed for Mn levels. Additionally, participants will be asked to complete questionnaires enquiring about their demographic information, mood, diet, occupational history, behavioral habits, and health history. Data collected from East Liverpool participants will be compared with previously collected data from the demographically similar, but less Mn-exposed town of Marietta, Ohio and the comparison town of Mount Vernon, Ohio where Mn exposure is not of concern.

The present study and its protocols have already been approved by SFSU Institutional Review Board (IRB) (see enclosed approval form). The study also has been described to all of the interested and collaborating stake holders (Ohio Department of Health, Ohio EPA, resident groups, health department officials, etc.) and the U.S.EPA and ATSDR.

A.4.2. **Purpose and Rationale**. Provide a summary of the background information, state the research question(s), and tell why the study is needed. If a complete rationale and literature review are in an accompanying grant application or other type of proposal, only provide a brief summary here. If there is no proposal, provide a more extensive rationale and literature review, including references.

For a more detailed description, please see the enclosed proposal.

Manganese is a naturally occurring essential element and low levels of Mn in water, food, and air are ubiquitous. In the occupational health literature there are many reports of workers exposed to Mn with adverse health effects. Miners, steel and alloy smelters, chemical plant workers over-exposed to Mn, and iron/steel welders are known to be at risk for developing a pattern of signs and symptoms showing a decline in psychiatric health (i.e. mood disturbance), deterioration of cognitive ability (i.e. problems with attention, memory, and information processing), and a movement disorder similar to Parkinson's disease (PD) (i.e. a disturbance of gait, loss of balance, dystonia, bradykinesia, and tremor) (Bowler et al., 2007).

Environmental studies of airborne Mn have been relatively rare and results of a select few studies have been published. Although recent studies on children exposed to Mn- through

drinking water show decrements in neuropsychological performance, none of the recent environmental studies on adults included comprehensive neuropsychological function testing in residents of living areas with air measurements, such as those detailed in the East Liverpool air reports. Only the earlier work by Mergler et al. (1999) related Mn in air to neuropsychological function. This present study seeks to fill that gap and will utilize past knowledge gained from these studies by using a more refined and recently updated neuropsychological test battery in addition to geo-coded data in relation to the Mn air results already performed by ATSDR and EPA in East Liverpool, Ohio.

The proposed study aims to answer the following questions:

- Is external Mn exposure (Mn-air) associated with biomarkers of internal Mn dose [Mn in blood (Mn-B), toenails (Mn-T), hair (Mn-H)] and neuropsychological and neurological function in adults?

- Does the neuropsychological function of a group of Mn-exposed adults differ significantly between groups with different levels of exposure to Mn-air?

This study will contribute to the knowledge of effects of environmental exposure at different levels to airborne Mn on neurological and neuropsychological functions of randomly selected adults.

A.4.3. **Subjects.** *You should describe the subject population even if your study does not involve direct interaction (e.g., existing records).* Specify number, gender, ethnicity, race, and age. Specify whether subjects are healthy volunteers or patients. If patients, specify any relevant disease or condition and indicate how potential subjects will be identified. Researchers are reminded that additional approvals may be needed from relevant "gatekeepers" to access subjects (e.g., school principals, facility directors, hospital or healthcare system administrators).

The proposed health study will recruit 100 individuals residing within 2.5 miles of the Water Plant air monitor in East Liverpool, Ohio. Due to the similarities between East Liverpool and the two communities already studied (Marietta, Ohio and Mount Vernon, Ohio), the selected participants are expected to be similar on age, gender, ethnicity, and level of education (see Appendix C of the enclosed proposal).

A.4.4. **Inclusion/exclusion criteria.** List required characteristics of potential subjects, and those that preclude enrollment or involvement of subjects or their data. Justify exclusion of any group, especially by criteria based on gender, ethnicity, race, or age. If pregnant women are excluded, or if women who become pregnant are withdrawn, specific justification must be provided.

**Inclusion criteria**

To be included in the study, participants must be 30-75 years old and have 10 years or more of residency in East Liverpool. Participants must live in homes serviced by the municipal water supply and must reside within two miles of the Water Plant air monitor in East Liverpool, Ohio.

**Exclusion criteria**

1. Having had a major occupational exposure to pesticides, fungicides, or herbicides, carbon monoxide (CO), or other toxic metals requiring a medical visit;
2. A diagnosis of a psychiatric, neurological, or hepatic medical condition, including: stroke, electroconvulsive treatment, epilepsy, brain surgery, encephalitis, meningitis, multiple

sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's dementia, schizophrenia, bipolar disorder;
3. Current treatment for alcohol or drug dependence;
4. Prior head injury or a stroke resulting in hospitalization for more than 1 day;
5. Having worked at S.H. Bell or Eramet Marietta Inc. at any time;
6. Women who are pregnant or nursing.

Pregnant and nursing women are excluded from the present study due to naturally occurring elevated levels of manganese in blood related to fetal development during pregnancy and the nutritional demands of breastfeeding. Mn biomarker results obtained from pregnant or nursing women would, therefore, not be representative of the community at large and would confound the interpretation of the data.

A.4.5. **Full description of the study design, methods and procedures.** Describe the research study. Discuss the study design; study procedures; sequential description of what subjects will be asked to do; assignment of subjects to various arms of the study if applicable; doses; frequency and route of administration of medication and other medical treatment if applicable; how data are to be collected (questionnaire, interview, focus group or specific procedure such as physical examination, venipuncture, etc.). Include information on who will collect data, who will conduct procedures or measurements. Indicate the number and duration of contacts with each subject; outcome measurements; and follow-up procedures. If the study involves medical treatment, distinguish standard care procedures from those that are research. If the study is a clinical trial involving patients as subjects and use of placebo control is involved, provide justification for the use of placebo controls.

**Study Design:** The proposed health study will utilize a cross-sectional design using a Mn-exposed group of 100 residents of East Liverpool drawn at random as an add-on to the 100 exposed residents from Marietta and 90 comparison residents from Mt. Vernon, who are part of a prior study currently being completed. As for the prior study, the same age group (30-75 years of age), and the same methods of selection/recruitment, inclusion and exclusion criteria, and neurological and neuropsychological test measures and procedures will be used in this current study of East Liverpool, Ohio.

**Data collection methods:** The same carefully controlled and standardized test administration instructions as those used in the Marietta/Mt Vernon study will be applied to the data collection procedures in East Liverpool. To the extent possible, the testers will be the same as in the prior study.

The data collected in this study will include the following:
1. Air exposure of Mn, already collected by the EPA/ATSDR for the period between 1999 and 2009 (9 years and 8 months).
2. Neuropsychological (including mood and motor efficiency) tests (see Appendix B of the enclosed proposal).
3. Neurological function will be assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) administered by the same trained physician (2 subscales: Activities of Daily Living and Motor Function)
4. The CATSYS (Danish Product Development) – consisting of 4 postural sway conditions and hand tremor.
5. A health questionnaire containing sections on residency, symptoms, medical history, medications, work history and behaviors, diet, and personal demographic information (enclosed).
6. The possibility of worry impacting symptom reporting in the East Liverpool group will be addressed in two ways: A) we will include an Environmental Worry Scale (EWS, enclosed),

scores of which will be analyzed as a potential confounder and B) all examiners will be (most already are) trained in detecting symptom and cognitive impairment exaggeration. Additionally, a short test of effort (Rey-15) will be administered, which if failed, will result in the administration of a highly regarded test of symptom validity, the Victoria Symptom Validity Test (VSVT). This test is designed to provide evidence that can confirm or disconfirm the validity of an examinee's cognitive and symptom impairments. In the event that the examinee fails both the Rey 15 and the VSVT, that participant's test scores will be excluded from the group analysis.

7. Whole blood will be analyzed for levels of manganese (Mn), mercury (Hg), cadmium (Cd), and lead (Pb) and serum will be used to evaluate ferritin and the liver enzymes, alanine-aminotransferase (ALT) and gamma-glutamyltransaminase (GGT). Toenail and hair samples will be analyzed for levels of Mn. In total, 12 mL whole blood will be collected from each participant for analyses. Whole blood samples will be shipped on dry ice by Fed Ex immediately to the CDC and serum samples to the U.S. EPA NHEERL Core laboratories. The samples will be identified by each participant's ID number only and no names will be included

**RECRUITMENT**

Participant recruitment will be preceded by public announcements of the study. The recruitment plan is outlined below.

**a) Community Meetings and Health Study Announcements**

1. Community meeting announcements will be made via radio, newspaper, and television.
2. The study P.I. and her assistant will travel to East Liverpool on September 14th, 2011 to meet with the Health Commissioner and her board, on September 15, 2011, presenting the study. The same evening, a meeting for the community will be held to describe the study as outlined below in # 3 open to the residents and other interested parties of East Liverpool.
3. The community meeting in East Liverpool will consist of a presentation of a brief slide show, previously presented at the Marietta, Ohio community meeting but revised for East Liverpool. Around the time of the community meeting, invitation letters will be mailed to all the residents within a 1 mile radius from the Water Tower air monitor and to a random sample of approximately 1/3 of the residents in the 1-2.5 mile area, selected at random form a purchased list of postal addresses. The letter will describe the East Liverpool Community Health Study and its procedures. The letters will also contain a stamped, self-addressed postcard where residents will be able to indicate their interest in study participation if they are eligible (determined by a phone call interview after the cards are received in the research office).

**b) Recruitment Procedure:**

1. The sample of households in the area of 2.5 miles surrounding the East Liverpool Water Plant air monitor and S.H. Bell will be obtained from the 911 database, and a purchased list of all complete postal addresses.
2. Letters will be mailed to all residents within the 1 mile area from the Water Plant air monitor and a randomly selected group of addresses representing 1/3 of the database containing the postal addresses for the 1-2.5 mile area. The letters will contain a self-addressed, stamped card which could be used to indicate willingness to participate or denial to participate in the health study. If participants indicated interest, a brief questionnaire listing the exclusion factors will be administered during subsequent telephone calls to the participants. If the number of return cards received 2 weeks after

the mail out is insufficient, the research team will attempt to contact potential participants via telephone. In an attempt to reach potential participants, a maximum of three phone calls will be made to those who have an answering machine and a maximum of five phone calls for those who do not have an answering machine. The telephone numbers will be obtained from an East Liverpool telephone book or the white pages. If the responses are insufficient in number, this process will be repeated until 110 adults are available to be tested or until the maximum number of phone calls has been reached for each potential participant (10 alternates are included to be called if any of the first 100 participants cannot come in the last few days prior to the appointment).

3. Calls will be made until 110 individuals agree to participate.
4. Selected participants will be contacted by telephone 4 weeks prior to the study to set up appointments at a convenient location.
5. Two days prior to the appointment, telephone appointment reminder calls will be made.
6. Because of concern and interest about chemical exposure, a relatively high response rate of ~50% is expected in East Liverpool.

**STUDY PROCEDURES**

**1.** The above recruitment methods will be followed.

**2.** Examiners will meet the day prior to testing and set up testing areas, review all test administrations and set up stations and offices where consent forms, interviews, and tests will be administered.

**3.** At the time the study will begin, scheduled study participants in groups (three groups per day) of 11 people (+ 1 extra person on one of the days) will be seated in a common area and greeted by the P.I. who will give a brief introduction about the study, the procedures, and the consent form.

**4.** The P.I. will interview all of the participants with a brief, somewhat structured interview schedule, asking participants about special concerns, fears and observations related to their exposure. The check-out staff person will at this time collect and de-identify the participant's list of current medications, (copied each night at the conclusions of testing) which will be hand-carried in carry-on luggage by the P.I.

**5.** Trained examiners will introduce themselves to participants and will explain the consent form in detail. Participants will be given time to ask questions. Then two copies of the informed consent will be signed; one for the participant and one for the researcher.

**6.** The participant will be invited to accompany one of the testers to a private room for testing. The neuropsychological testing will be conducted without any identifiers on the test protocols other than the respective I.D. number. Examiners will be two neuropsychologists and six graduate students in psychology, who will be trained by the P.I. and senior staff (all have completed the course for the protection of human subjects – certificates enclosed).

**7.** After completion of the tests, the study staff will introduce participants to the certified phlebotomist, who will draw a total of 12 mL of venous blood from each participant for analysis. The Centers for Disease Control and Prevention (CDC) Environmental Health Laboratory has agreed to perform the blood analyses of whole blood for Mn, Pb, Cd, and Hg levels. Ferritin levels, and ALT and GGT activities in serum will be determined by the U.S. EPA NHEERL Core laboratories. A total of 200 samples (two vials per participant, 6 mL each) of whole blood will be collected from study participants by the licensed and trained phlebotomist/medical technician. Presumably, one needle stick per participant (or as few as needed) will be used by the certified phlebotomist/medical technician. Four mL of whole blood will then be centrifuged at 800 x g for 10 min at

room temperature to separate the serum. Whole blood will be kept at 4°C and serum samples will be immediately stored at -18°C until analysis and sent weekly by Express Mail to the laboratory. Half a milliliter of serum is needed for the analysis of ferritin concentrations by immunoturbidity using the Roche Tina-quant assay on the Hitachi 912 clinical analyzer. Also half a milliliter of serum is needed to analyse the activities of the liver enzymes ALT and GGT with a Beckman Synchron LX20 using an enzymic rate method. The usual QA/QC methods of the CDC Laboratory will be applied. Each analytic run is surrounded by at least two levels of bench quality control and one blind quality control sample is inserted with each run (40-60 samples). The methods are CLIA-certified and multiple PT are run, as available. The DLS QA/QC system (Caudill et al., 2008) is referred to as the Multi-Rule Quality Control System (MRQCS). The CDC rules are similar in nomenclature to Westgard's format, but the rules are not identical. Some of the additional features of MRQCS include the ability to distinguish between within-run and among-run precision, accommodating variable numbers of QC measurements per run and accommodating variable numbers of QC samples per pool. Quality control measures include analysis of initial calibration verification standard (National Institute of Standard and Technology standard reference material (NIST SRM) 1643e (trace elements in water, Gaithersburg, MD), a solution of NIST traceable 1 ng $ml^{-1}$ manganese standard as the continuous calibration verification standard, procedural blank and Certified Reference material GBW 07601 (human hair) (Institute of Geophysical and Geochemical Exploration, Langfang, China) will be used as the quality control sample. Results will be given as the average of five replicate measurements of the instrument. Recovery of the analysis of QC standard by this procedure is 90% -110% and, precision is given as %RSD (SD*100/Mean) and for hair samples it varied from 1%-25%.

8. Hair samples will be collected using the following procedures: The collector will first evaluate the presence of sufficient hair on head for collection. Approx. 1-3 cm of hair should be available for collection. The scissors will be cleaned with an alcohol swab in front of the participant. Hair will be cut as close to the skull as possible from the base of the skull near the point halfway between the spine & ear (lower right or left quadrant). When enough mass is an issue, typically on men, smaller snips of hair will be taken in a random pattern. The side of hair sample that was close to the scalp will be marked by tying that end off with sewing thread and the collected hair will be placed into a small plastic bag with the participant's id clearly indicated on the bag. All small bags will be sealed and placed into a container and sent to the laboratory for analysis.
9. Toenail samples will be collected in the following manner: A pair of titanium dioxide nail clippers will be rubbed with alcohol swabs to be thoroughly cleaned between people. Participants will be asked to clip their nails from all ten toes onto a clean paper (to make it easier to catch all the clippings) and place the collected nails in a small plastic bag labeled with their respective ID. All small bags will be placed into a container and send to the laboratory for analysis.

   Whole sample (Hair/Toenails) will be pre-cleaned with 1% Triton X-100 solution prior to analysis to remove extraneous contaminants. Samples will be acid digested using ultra pure nitric acid at room temperature for 24 hours. Diluted samples will be analyzed for manganese using inductively coupled plasma mass spectrometry (ICP-MS, DRC-II, Perkin Elmer, Norwark, CT) using indium as the internal standard.
10. Two post-baccalaureate level students who were also part of the testing team in Marietta and Mt. Vernon, OH, will conduct check-in and check-out and review the questionnaires and individual participant folders to ascertain that all tests have been completed before the participant leaves. This protocol completeness review will be performed in order to

detect unintentional omissions. Participants will at no time be pressured to answer any items they choose not to answer.

**11.** Upon completion of the study, a gift card for $50.00 for a local store will be presented to each participant as a token of appreciation for participation in the study.

**12.** Feedback of the group's results will be given to the community and all interested parties either in person or in written form during late summer of 2012. If additional funding becomes available, the P.I. will also present group results of the study in a community meeting in East Liverpool.

**13.** After the conclusion of the study, a brief feedback report will be prepared and mailed to each participant reporting the individual's test scores (by domain of function) and results of biomarker analyses. This report will also indicate whether the test results were:

a) within the normal range
b) of concern, needing a referral to the family physician for further assessment by specialists as indicated.

**14.** All relevant professional parties and city officials will be contacted and given feedback of the group's findings.

**15.** All inquiries by the media will be answered by the team of investigators including the P.I., Mr. Greg Stein from ODH and Dr. George Bollweg, representing the Regional U.S. EPA. Prior to any release of data, results and talking points will have been presented to the entire group of investigators, collaborators and advisory board for input and final wording.

A.4.6. **Benefits to subjects and/or society.** Describe any potential for direct benefit to individual subjects, as well as the benefit to society based on scientific knowledge to be gained; these should be clearly distinguished. Consider the nature, magnitude, and likelihood of any direct benefit to subjects. If there is no direct benefit to the individual subject, say so here and in the consent form (if there is a consent form). Do not list monetary payment or other compensation as a benefit.

**Direct benefits to subjects**

There are no direct benefits to participants.

**Benefits to society**

The study will address concerns about the potential health effects of Mn exposure by assessing the health status of a representative sample of East Liverpool residents. The study will provide important information about potential effects of gradients of exposure to Mn from industrial sources in non-occupational environmental settings. Furthermore, the study will add to the limited literature on the relationship between various biomarkers of Mn (blood, toenails, hair).

A.4.7. **Full description of risks and measures to minimize risks.** Include risk of psychosocial harm (e.g., emotional distress, embarrassment, breach of confidentiality), economic harm (e.g., loss of employment or insurability, loss of professional standing or reputation, loss of standing within the community) and legal jeopardy (e.g., disclosure of illegal activity or negligence), as well as known side effects of study medication, if applicable, and risk of pain and physical injury. Describe what will be done to minimize these risks. Describe procedures for follow-up, when necessary, such as when subjects are found to be in need of medical or psychological referral. If there is no direct interaction with subjects, and risk is limited to breach of confidentiality (e.g., for existing data), state this.

- Drawing venous blood from the arm may cause minimal pain when the needle is inserted. There is also a slight risk of bruising and infection where the needle punctures the skin. In rare cases, some people may experience lightheadedness, nausea, or fainting. The certified phlebotomist is trained in recognizing and dealing with these types of reactions.

All possible accommodations will be made should this occur. Cutting a small amount of hair will be done with a blunted scissors which will prevent any accidental injuries. Blood samples will also be marked with an ID number only to ensure those analyzing the blood/serum are blinded to the identity of the participant. Arrangements will be made with a local physician on call, who will be recruited by a local colleague practicing in East Liverpool. The pager number and location of this local physician will be obtained so he/she may be contacted and available to address any medical emergency that may arise. Although such emergencies are highly unlikely, a participant, if necessary can be brought to the nearest Emergency Room at the local hospital.

- There is a risk of experiencing slight fatigue during testing. Testers are trained to look for signs of fatigue and a break will promptly be offered. The participants will also be informed that they can take a break or discontinue testing at any point.
- Participation may involve potential loss of privacy. To minimize this, results will be stored in a password-protected computer database with no identifying information attached. Hard copy files of all of the data will be kept by the P.I. in a locked file cabinet for 5 years with documents containing ID numbers only. Any documents or computer files linking ID numbers to names will be kept in a separate, locked file cabinet (or computer database) only accessible by the P.I. and will also be destroyed after 5 years.

A.4.8. **Data monitoring and analysis.** Tell how the qualitative and/or quantitative data will be analyzed. Explain how the sample size is sufficient to achieve the study aims. This might include a formal power calculation or explanation of why a small sample is sufficient (e.g., qualitative research, pilot studies). Describe the provisions for monitoring the data to ensure the safety of participants. These plans could range from the investigator monitoring subject data for any safety concerns to a sponsor-based DSMB, depending on the study.

In order to compare scores on neuropsychological, motor and mood tests, and the UPDRS between the three towns, the general linear model will be used. This will test for differences between participants in the three towns, including pairwise comparisons for differences in domains of neurological, neuropsychological, mood and motor functioning, with covariates included in the model as necessary. Logistic regressions will be used for dichotomous outcomes such as symptom and illness frequencies in each town, comparing the relative risk between the samples after controlling for the effects of covariates.

Multiple regression analyses will test for relationships between Mn levels in air, blood, hair, and toenails, and neuropsychological test scores in East Liverpool, and these relationships will be compared to the results recently obtained in Marietta. Logistic regressions will be used for categorical outcomes to examine the relationship between Mn levels in air and risk for particular illnesses or symptoms and mood.

Power analyses using G*Power statistical software indicated adequate statistical sensitivity with a sample size of 100. Setting power at 0.80 and alpha at 0.05, one-way between groups analyses of means would be powered to detect an effect size of f=.18 or greater. This is halfway between a small and medium effect size based on Cohen's (1988) guidelines, and should be sufficiently sensitive to detect the effects of manganese exposure in this sample, based on theory and previous research.

A.4.9. **Will you collect or receive any of the following identifiers?** Does not apply to consent forms.

__ No _**X**_ Yes *If yes, check all that apply*:

a. _**X**_ Names
b. _**X**_ Telephone numbers
c. _**X**_ Any elements of dates (other than year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death. For ages over 89: all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 and older
d. _**X**_ Any geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code
e. __ Fax numbers
f. _**X**_ Electronic mail addresses
g. __ Social security numbers
h. __ Medical record numbers
i. __ Health plan beneficiary numbers
j. __ Account numbers
k. __ Certificate/license numbers
l. __ Vehicle identifiers and serial numbers (VIN), including license plate numbers
m. __ Device identifiers and serial numbers (e.g., implanted medical device)
n. __ Web universal resource locators (URLs)
o. __ Internet protocol (IP) address numbers
p. __ Biometric identifiers, including finger and voice prints
q. __ Full face photographic images and any comparable images
r. __ Any other unique identifying number, code, or characteristic, other than dummy identifiers that are not derived from actual identifiers and for which the re-identification key is maintained by the health care provider and not disclosed to the researcher

A.4.10. **Identifiers in research data**. Are the identifiers in A.4.9 above linked or maintained with the research data?

__ yes _X_ no – only nonidentifiable ID numbers will be associated with the research data

A.4.11. **Confidentiality of the data**. Describe procedures for maintaining confidentiality of the data you will collect or will receive. Describe how you will protect the data from access by those not authorized. How will data be transmitted among research personnel? Where relevant, discuss the potential for deductive disclosure (i.e., directly identifying subjects from a combination of indirect IDs).

All test results will be linked to an ID number, with all personally identifying participant information removed. Results will be stored in an encrypted document on a password-protected computer and all paper materials will be stored in a locked file cabinet in the P.I.'s research office laboratory at 8371 Kent Drive, El Cerrito, CA 94530. Only Dr. Bowler will have access to information linking ID numbers and the identities of the participants. Each page in the participant's folder will be coded with an ID number only.

Security will be maintained by having an alarm system in the building and by having each staff member sign a special Data Contract to maintain confidentiality of the data, refraining from any public conversations about the participants. The data will not be released unless subpoenaed by a court of law. Anyone working on the data will also be required to sign this, guaranteeing confidentiality and guaranteeing that these data will not be used unless the P.I. is involved in order to guarantee privacy to the information given by the participant. All data will be maintained for approximately 5 years in hard copy, limiting access to only authorized individuals. The electronic data will be securely stored indefinitely. Unauthorized access will be

reported to the relevant parties (IRB, participants, stakeholders). Electronic data will be saved on a device that has the appropriate security safeguards, such as unique identification of authorized users, password protection, automated operating system patch (bug fix) management, anti-virus controls, firewall configuration, and scheduled and automatic backups to protect against data loss.

A.4.12. **Data sharing.** With whom will *identifiable* (contains any of the 18 identifiers listed in question A.4.9 above) data be shared outside the immediate research team? For each, explain confidentiality measures. Include data use agreements, if any.

**_X_** No one
__ Coordinating Center**:**
__ Statisticians**:**
__ Consultants**:**
__ Other researchers**:**
__ Registries**:**
__ Sponsors:
__ External labs for additional testing:
__ Journals:
__ Publicly available dataset:
__ Other:

A.4.13. **Data security for storage and transmission**. Please check all that apply.

*For electronic data stored on a desk top computer:*
_X_ Secure network _X_ Password access __ Data encryption_X_ Password protected file(s)
__ Other comparable safeguard (describe):

*For portable computing devices/external storage devices (e.g. laptop computer, PDA, CDs, memory sticks):*
_X_ Power-on password __ Automatic log-off __ Data encryption _X_ Password protected file(s)
__ Other comparable safeguard (describe):

*For hardcopy data (including human biological specimens, CDs, tapes, etc.):*
_X_ Data de-identified by research team (stripped of the 18 identifiers listed in question A.4.9 above)
_X_ Locked suite or office _X_ Locked cabinet and Security Alarm in the Research Building
_X_ Data coded by research team with a master list secured and kept separately
__ Other (describe):

A.4.14. **Post-study disposition of identifiable data or human biological materials**. Describe your plans for disposition of data or human biological specimens that are identifiable in any way (directly or via indirect codes) once the study has ended. Describe your plan to destroy identifiers, if you will do so.

The CDC and US EPA laboratories are using the federally approved guidelines for maintenance and destructions of human biological specimens. All hard copies of data, including the list linking ID

numbers with the names of participants, will be destroyed by shredding 5 years after the completion of the study.

## Part A.5. The Consent Process and Consent Documentation (including Waivers)

The standard consent process is for all subjects to sign a document containing all the elements of informed consent, as specified in the federal regulations. Some or all of the elements of consent, including signatures, may be altered or waived under certain circumstances.

- If you will obtain consent in any manner, complete **section A.5.1**.
- If you are obtaining consent, but requesting a waiver of the requirement for a signed consent document, complete **section A.5.2**.
- If you are requesting a waiver of any or all of the elements of consent, complete **section A.5.3**.
- If you need to access Protected Health Information (PHI) to identify potential subjects who will then be contacted, you will need a *limited waiver of HIPAA authorization*. This is addressed in section B.2.

You may need to complete more than one section. For example, if you are conducting a phone survey with verbal consent, complete sections A.5.1, A.5.2, and possibly A.5.3.

A.5.1. **Describe the process of obtaining informed consent from subjects**.
Describe who will be obtaining consent (or permission) and from whom. Include discussion, as relevant, any waiting period between the initial consent discussion and obtaining consent, and steps that will be taken to minimize coercion or undue influence. If children will be enrolled as subjects, describe the provisions for obtaining parental permission and assent of the child. If decisionally impaired adults are to be enrolled, describe the provision for obtaining surrogate consent from a legally authorized representative (LAR). If non-English speaking people will be enrolled, explain how consent in the native language will be obtained. Address both written translation of the consent and the availability of oral interpretation. It is expected that the information in the consent document(s) will be communicated to participants or their LAR. *After you have completed this part A.5.1, if you are not requesting a waiver of any type, you are done with Part A.5.; proceed to Part B.*

The study will first be introduced to East Liverpool residents at the community meeting that will take place in September 2011. A slide show detailing the study procedures for the community residents will be presented. Residents will be informed that they might receive a letter from the P.I. containing the study description. If selected, residents will be asked to complete and return a stamped, self-addressed card indicating willingness or non-willingness to participate to the P.I. Participants will be able to have their questions answered during the recruitment and screening calls, as well as later, at the time of the appointment. They will be able to ask the P.I. any additional questions that may arise either on site after the meeting or over the telephone when they are administered the inclusion/exclusion questionnaire. They also will be provided additional time to ask questions when the IRB approved consent forms are explained and reviewed by the examiners with each participant at the time of testing. The consent forms will be kept in each participant's testing protocol folder for the duration of the study procedure. Upon arrival at the P.I.'s office, the consent forms will be removed from the folders containing the participants' test protocols and will be in possession of the P.I. , along with the list connecting IDs and names. These forms will be kept in a locked file cabinet in the P.I.'s office.

A.5.2. **Justification for a waiver of *written* (i.e., signed) consent**. *The default is for subjects to sign a written document that contains all the elements of informed consent.* Under limited circumstances, the requirement for a signed consent form may be waived by the IRB if either of the following is true. *Choose only one:*

a. The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality (e.g., study topic is sensitive so that public knowledge of participation could be damaging). *Participants should be asked whether they want documentation linking them with the research and the participants' wishes will govern whether they sign the form.* Note: This justification cannot be used in FDA-regulated research. __ yes __ no __ yes __ no

**Explain.**

b. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context (e.g., phone survey).

**Explain.**

*If you checked "yes" to either (and you are not requesting a waiver in section A.5.3) consent must be obtained orally, by delivering a fact sheet, through an online consent form, or be incorporated into the survey itself. Include a copy of the consent script, fact sheet, online consent form, or incorporated document.*

→ If you have justified a waiver of written (signed) consent (A.5.2), you should complete A.5.3 *only* if your consent process will not include all the other elements of consent.

A.5.3. **Justification for a full or partial waiver of consent.** *The default is for subjects to give informed consent.* A waiver might be requested for research involving only existing data or human biological specimens (see also Part C). More rarely, it might be requested when the research design requires withholding some study details at the outset (e.g., behavioral research involving deception). In limited circumstances, parental permission may be waived. This section should also be completed for a waiver of HIPAA authorization if research involves Protected Health Information (PHI) subject to HIPAA regulation, such as patient records.

__ Requesting **waiver of some elements** (specify; see SOP 28 on the IRB web site):
__ Requesting **waiver of consent entirely**
If you check either of the boxes above, answer items a-f.. To justify a full waiver of the requirement for informed consent, you must be able to answer "yes" (or "not applicable" for question c) to items a-f. **Insert brief explanations that support your answers.**

a. Will the research involve no greater than minimal risk to subjects or to their privacy? __ yes __ no

**Explain.**

b. Is it true that the waiver will *not* adversely affect the rights and welfare of subjects? *(Consider the right of privacy and possible risk of breach of confidentiality in light of the information you wish to gather.)* __ yes __ no

**Explain.**

c. When applicable to your study, do you have plans to provide subjects with pertinent information after their participation is over? *(e.g., Will you provide details withheld during consent, or tell subjects if you found information with direct clinical relevance? This may be an uncommon scenario.)* __ yes __ not applicable

**Explain**.

d. Would the research be impracticable without the waiver? *(If you checked "yes," explain how the requirement to obtain consent would make the research impracticable, e.g., are most of the subjects lost to follow-up or deceased?).* __ yes __ no

**Explain.**

e. Is the risk to privacy reasonable in relation to benefits to be gained or the importance of the knowledge to be gained? __ yes __ no

**Explain.**

**If you are accessing patient records for this research, you must also be able to answer "yes" to item f to justify a waiver of HIPAA authorization from the subjects.**

f. Would the research be impracticable if you could not record (or use) Protected Health Information (PHI)? *(If you checked "yes," explain how* not *recording or using PHI would make the research impracticable).* __ yes __ no

**Explain.**

## Part B. Questions for Studies that Involve Direct Interaction with Human Subjects

→ ***If this does not apply to your study, do not submit this section.***

B.1. **Methods of recruiting.** Describe how and where subjects will be identified and recruited. Indicate who will do the recruiting, and tell how subjects will be contacted. Describe efforts to ensure equal access to participation among women and minorities. Describe how you will protect the privacy of potential subjects during recruitment. *For prospective subjects whose status (e.g., as patient or client), condition, or contact information is not publicly available (e.g., from a phone book or public web site), the initial contact should be made with legitimate knowledge of the subjects' circumstances. Ideally, the individual with such knowledge should seek prospective subjects' permission to release names to the PI for recruitment. Alternatively, the knowledgeable individual could provide information about the study, including contact information for the investigator, so that interested prospective subjects can contact the investigator.* Provide the IRB with a copy of any document or script that will be used to obtain the patients' permission for release of names or to introduce the study. Check with the IRB for further guidance.

Full descriptions of the study design, methods and procedures are included in the enclosed proposal. Participant recruitment will be preceded by public announcements of the study. The recruitment plan is outlined below.

**a) Community Meetings and Health Study Announcements**

4. Community meeting announcements will be made via radio, newspaper, and television.
5. The study P.I. and her assistant will travel to East Liverpool on September 14th, 2011 to meet with the Health Commissioner and her board, on September 15, 2011, presenting the study. The same evening, a meeting for the community will be held to describe the study as outlined below in # 3 open to the residents and other interested parties of East Liverpool.
6. The community meeting in East Liverpool will consist of a presentation of a brief slide show, previously presented at the Marietta, Ohio community meeting but revised for East Liverpool. Around the time of the community meeting, invitation letters to a large random sample of approximately 1/3 East Liverpool households, selected at random form a purchased list of postal addresses within two miles of the Water Plant air monitor will be mailed. The letter will describe the East Liverpool Community Health Study and its procedures. The letters will also contain a stamped, self-addressed postcard where residents will be able to indicate their interest in study participation if they are eligible (determined by a phone call interview after the cards are received in the research office).

**b) Recruitment Procedure:**

7. The sample of households in the area of two miles surrounding the East Liverpool Water Plant air monitor and S.H. Bell will be obtained from the 911 database, and a purchased list of all complete postal addresses for the 2 mile area west of the Water Tower Monitor and the S.H. Bell facility.
8. Letters will be mailed to a randomly selected group of addresses representing 1/3 of the database containing the postal addresses. The letters will contain a self-addressed, stamped card which could be used to indicate willingness to participate or denial to participate in the health study. If participants indicated interest, a brief questionnaire

listing the exclusion factors will be administered during subsequent telephone calls to the participants. If the number of return cards received 2 weeks after the mail out is insufficient, the research team will attempt to contact potential participants via telephone. In an attempt to reach potential participants, a maximum of three phone calls will be made to those who have an answering machine and a maximum of five phone calls for those who do not have an answering machine. The telephone numbers will be obtained from an East Liverpool telephone book or the white pages. If the responses are insufficient in number, this process will be repeated until 110 adults are available to be tested or until the maximum number of phone calls has been reached for each potential participant (10 alternates are included to be called if any of the first 100 participants cannot come in the last few days prior to the appointment).

9. Calls will be made until 110 individuals agree to participate.
10. Selected participants will be contacted by telephone 4 weeks prior to the study to set up appointments at a convenient location.
11. Two days prior to the appointment, telephone appointment reminder calls will be made.
12. Because of concern and interest about chemical exposure, a relatively high response rate of ~50% is expected in East Liverpool.

B.2. **Protected Health Information (PHI).** If you need to access Protected Health Information (PHI) to identify potential subjects who will then be contacted, you will need a *limited waiver of HIPAA authorization*. If this applies to your study, please provide the following information and complete Section C.

This study does not require a HIPPA consent form. We are not obtaining medical records, nor using medical data from those records.

a. Under this limited waiver, you are allowed to access and use only the minimum amount of PHI necessary to review eligibility criteria and contact potential subjects. What information are you planning to collect for this purpose?

b. How will confidentiality/privacy be protected prior to ascertaining desire to participate?

c. When and how will you destroy the contact information if an individual declines participation?

B.3. **Duration of entire study and duration of an individual subject's participation, including follow-up evaluation if applicable.** Include the number of required contacts and approximate duration of each contact.

The study will take place over the course of 12 months and will include preparation, testing (data collection), data entry, data cleaning and analyses, and participant feedback and final reports. Participants might be directly involved in the study on the following occasions:

1. Receipt of a recruitment letter
2. Mailing of a stamped, pre-addressed postcard to indicate interest in participating
3. Screening telephone call – 10 min
4. Appointment scheduling telephone call – 5 min
5. Appointment reminder call – 3 min

6. Testing – 2.5- 4 hours
7. Receipt of feedback letter

B.4. **Where will the subjects be studied?** Describe locations where subjects will be studied, both on and off the UNC-CH campus.

The data collection part of the study (i.e. testing) will take place in a central location in East Liverpool, Ohio (the Motor Lodge Motel).

B.5. **Privacy.** Describe procedures that will ensure privacy of the subjects in this study. Examples include the setting for interviews, phone conversations, or physical examinations; communication methods or mailed materials (e.g., mailings should not indicate disease status or focus of study on the envelope).

To ensure privacy, all neuropsychological testing will be conducted in a private room with only the participant and examiner present. Collection of blood, toenail, and hair samples will also take place in a separate, private room, as will the CATSYS and UPDRS examinations. The P.I. will conduct a brief interview with each participant in a secluded area. No phone conversations with participants will be conducted in public – all phone conversations will take place in private office settings.

B.6. **Inducements for participation.** Describe all inducements to participate, monetary or non-monetary. If monetary, specify the amount and schedule for payments and if/how this will be prorated if the subject withdraws (or is withdrawn) from the study prior to completing it. For compensation in foreign currency, provide a US$ equivalent. Provide evidence that the amount is not coercive (e.g., describe purchasing power for foreign countries). Be aware that payment over a certain amount may require the collection of the subjects' Social Security Numbers. If a subject is paid more than $200.00 per year, collection of subjects' Social Security Number is required (University policy—see SSN Guidance) using the Social Security Number collection consent addendum found under forms on the IRB website (look for Study Subject Reimbursement Form).

Upon completion of the study, a gift card for $50.00 from a local store will be presented to each participant as a token of appreciation for participation in the study. This amount is not considered coercive. Due to limited funding, early withdrawal from the study or incompletion of major parts of the study will not be compensated monetarily.

B.7. **Costs to be borne by subjects.** Include child care, travel, parking, clinic fees, diagnostic and laboratory studies, drugs, devices, all professional fees, etc. If there are no costs to subjects other than their time to participate, indicate this.

There is no cost for taking part in the study, aside from the transportation costs of coming to the appointment. Transportation costs involved in coming to the facility, which will be selected to be convenient for participants, will not be reimbursed. The researchers, research team and sponsors of this project will not provide medical care nor cover the cost of medical care for participants.

## Part C. Questions for Studies using Existing Data, Records or Human Biological Specimens

→ ***This section applies even if records are only used to identify potential subjects.***

→ ***If your study does not use existing data, records or specimens for any purpose, do not submit this section.***

C.1. What records, data or human biological specimens will you be using? *(check all that apply)*:

_X_ Data already collected for another research study
If applicant was involved in the original collection, please explain role:

The P.I. of the present study was also the principal investigator of the Marietta/Mount Vernon Health study, data from which will be used in the data analyses phase of the present study.

__ Data already collected for administrative purposes (e.g., Medicare data, hospital discharge data)
__ Medical records (custodian may also require form, e.g., HD-974 if UNC-Health Care System)
__ Electronic information from clinical database (custodian may also require form)
__ Patient specimens (tissues, blood, serum, surgical discards, etc.)
_X_ Other (specify):
Completely de-identified research data from the prior Marietta/Mount Vernon health study will be used.

C.2. For each of the boxes checked in 1, how were the original data, records, or human biological specimens collected? Describe the process of data collection including consent, if applicable.

The data collection process for the Marietta/Mount Vernon Health study was identical to the one outlined in the present study, with the exception of not including toenail and hair sample collected. The protocol, consent forms and scripts were reviewed and approved by the San Francisco State University IRB, 2 external reviewers on behalf of the U.S. EPA, and the Ohio Department of Health.

C.3. For each of the boxes checked in 1, where do these data, records or human biological specimens currently reside?

The non-identifiable data is currently in possession of the P.I.

C.4. For each of the boxes checked in 1, do you have permission from the custodians of the data, records or human biological specimens (e.g., pathology dept, tissue bank, original researcher)? Include data use agreements, if required by the custodian of data that are not publicly available.

N/A

C.5. If the research involves human biological specimens, has the purpose for which they were collected been met before removal of any excess? For example, has the pathologist in charge or the clinical laboratory director certified that the original clinical purpose has been satisfied? Explain if necessary.

__ yes __ no _X_ not applicable (explain)

The specimens collected previously were part of an epidemiologic examination, NOT from patient specimen excess. All the specimens have been tested and only the results of the already tested specimens will be used in this study.

C.6. Do *all* of these data, records or specimens exist at the time of this application? If not, explain how prospective data collection will occur.

_X_ no If no, explain

**San Francisco State University 8/1/11**

**An Epidemiologic Health Study of Manganese Exposure in adult residents of**

**East Liverpool, Ohio**

**Researcher's Name: Rosemarie Bowler, Ph.D., M.P.H.**

**Department: Psychology**

## 1. STUDY AIM, BACKGROUND AND DESIGN

The proposed study aims to answer the following questions:

- Is external Mn exposure (Mn-air) associated with biomarkers of internal Mn dose [Mn in blood (Mn-B), toenails (Mn-T), hair (Mn-H)] and neuropsychological and neurological function in adults?
- Does the neuropsychological function of a group of Mn-exposed adults differ significantly between groups with different levels of exposure to Mn-air?

### Exposure Background:

On November 16, 2010 the U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR) presented residents of the town of East Liverpool, adjacent to the Ohio River, with an air quality report describing the potential health risks from ambient metals. Analyses of the U.S. EPA's air monitoring data at three locations in East Liverpool have shown elevated ambient air levels of manganese (Mn) and chromium-III (CrIII) over a period of nine years and eight months (between January 1999 and September 2009). Mn-air levels in East Liverpool (Water plant monitor) were found to be on average about 10 times higher than those in another Mn-exposed Ohio town (Marietta), which, along with a similar non-industrially Mn-exposed town (Mt. Vernon), has been examined recently in a health study conducted by the P.I. and her colleagues. Ohio EPA identified the S.H. Bell Company, a facility that warehouses and packages primarily raw metals (including Mn) from all over the world, as an exposure source contributing to these elevated levels. The present study seeks a) to determine the possible health risks to residents of the high Mn-exposure in East Liverpool, and b) to compare any health effects between the towns (exposed and comparison) currently being studied by this team of investigators.

There is a time urgency to perform a health study of the Mn health risks in East Liverpool because the S.H. Bell Company has been required by Ohio EPA to reduce the community's exposure to Mn emissions. In two Ohio EPA and US EPA enforcement actions, the plant was asked to comply with the following guidelines in order to remain in operation: pave a dirt road on the State Line property, install a dust suppression program, enclose some storage piles, improve dust collection, and tarp all trucks leaving the S.H. Bell facility. The site upgrades were completed in 2008 and it is anticipated that Mn-air will have decreased by the middle of 2011. Ohio EPA also plans to continue the air monitoring and, moreover, have already installed

a $PM_{10}$ monitor and plan to install a $PM_{2.5}$ monitor which will assess the respirable fraction of the Mn particles.

The experienced research team proposing this health evaluation is prepared to conduct such a study of East Liverpool residents on short notice because they have already developed epidemiologic methods and applied them in the current health study being completed of the Mn-exposed town of Marietta, Ohio and the unexposed comparison town of Mt. Vernon, Ohio. Relevant health questionnaires - including questions on demographic and residential history, symptoms and illnesses, environmental characteristics, such as intake of Mn and iron in diet, time spent indoors and outdoors - have already been developed and tested and are appropriate for use in East Liverpool with minimal changes. Ohio Department of Health has pledged to assist the P.I. and study investigators with news media co-ordination and lending state-level support to the study team. Additionally, Dr. Michelle Colledge, who authored the East Liverpool Air Quality Report of November 16, 2010, will collaborate on the analyses of the air Mn exposure (ATSDR, 2010). Advanced staff members from the ATSDR and the U.S. and Region 5 EPA will collaborate with the team of investigators, trained neuropsychological testers, medical experts, and statisticians who have been working conjointly on the Marietta-Mt. Vernon study. They will be available this calendar year (2011) and are willing to work on the proposed on-site applied health research study in East Liverpool. The proposed study offers the opportunity to examine an additional, more highly Mn-exposed community, and to compare the results to the two towns in Ohio under current study.

**Exposure source:**

Ambient air monitoring has already been conducted at three monitor locations near the S.H. Bell Company in East Liverpool and ambient Mn-air measurements are available from the Ohio EPA and the ATSDR for a period of nine years and eight months.

As described in the East Liverpool Air Quality Report by the ATSDR of November 16, 2010 (ATSDR, 2010), the S.H. Bell Company handles a great volume of raw and processed metal products. S.H. Bell has two locations in East Liverpool, approximately one mile apart: the Little England facility and the State Line facility. Ferrous and nonferrous materials are stored, transferred, and warehoused at both locations. The S.H. Bell Company is equipped to process, dry, crush, screen, and package their ore/materials for industry. Shipping occurs through river barge, truck, and rail. On most days, this includes shipping out 1.5 barges and 100-120 trucks (ATSDR Health Consultation report, 2010). Although the company employed 52 persons in 2007, by 2009, this number decreased to 26 workers. The results of air monitoring reported in the November 2010 East Liverpool Air Quality Report showed highly elevated Mn levels in air (ATSDR, 2010). Only two metals, Mn and Cr were identified as elevated in the air sampled over nine years and eight months. More specifically, all of the identified chromium particulate matter was CrIII – no CrVI was noted. CrIII is not associated with an increased cancer risk and is not considered to be a health concern (ATSDR, 2010). The EPA's computation of a hazard quotient (HQ: ambient concentration divided by the reference concentration of 0.05 $\mu g/m^3$) of 30 indicated the residences near the Water Plant air monitor (S.H. Bell State Line facility) have the highest non-cancer risk, with 99% of the risk "attributed to Mn" (ATSDR, 2010).

The monitors located near the two S.H. Bell facilities in East Liverpool are (See Appendix A of

this report and the Air Quality Report of November 16, 2010):

1. **Water Plant** monitor immediately adjacent to the S.H. Bell State Line facility. The air monitor is located approximately 250 feet W from the State Line facility with average Mn TSP concentration of 1.30 $\mu g/m^3$, range 0.10-23.0 $\mu g/m^3$

2. **Maryland Avenue** monitor located about 0.30 miles to the north-northwest of the S.H. Bell Little England facility – with average Mn TSP concentration of 0.18 $\mu g/m^3$, range 0.01-1.0 $\mu g/m^3$

3. **Port Authority** monitor located approximately 0.33 miles to the west-southwest of the S.H. Bell Little England facility with average Mn TSP concentrations of 0.26 $\mu g/m^3$, range 0.02-1.9 $\mu g/m^3$

Because the Water Plant monitor clearly shows the highest levels of Mn in air, the area around the water plant in a 2.5 mile radius will be the area studied under the proposed protocol. Additionally, census data indicates that this area has a sufficient number of housing units from which to recruit a random sample of 100.

The EPA has indicated that average Mn concentrations are between 0.04 and 0.05 $\mu g/m^3$ in urban areas. The ATSDR also reports average levels in urban areas of 0.05 $\mu g/m^3$ and the WHO reports concentrations near industrial Mn sites to be 0.2 to 0.3$\mu g/m^3$ . The area around the East Liverpool air monitors is densely populated, making it an ideal natural laboratory to study the health effects of moderately high levels of Mn in air in an environmental setting.

**Human Exposure to Manganese:**

Manganese is a naturally occurring essential element and low levels of Mn in water, food, and air are ubiquitous. Although Mn is also contained in food, it is thought to be more readily absorbed from water and air. In certain geographic regions, long contact between groundwater and Mn in bedrock can lead to high levels of Mn in water (U.S.EPA, 2004). Industrial plants involved in the refining and processing of Mn ore have higher Mn emissions, which may affect the health of humans residing in close proximity. The Mn exposure route of most concern in the present study is inhalation. Blood biomarkers will reflect all routes of Mn exposure. Diet will be surveyed with a suitable brief diet questionnaire to assess approximate intake of Mn rich foods such as nuts, beans and tea and whole grains (rice, wheat, oats, etc.), but Mn in diet is not considered to have a contribution to adverse health effects. The proposed study will also provide pilot data that will subsequently help conducting an even larger, more comprehensive study by ATSDR at a later date.

In the occupational health literature there are many reports of workers exposed to Mn with adverse health effects. Miners, steel and alloy smelters, chemical plant workers over-exposed to Mn, and iron/steel welders are known to be at risk for developing a pattern of signs and symptoms showing a decline in psychiatric health (i.e. mood disturbance), deterioration of cognitive ability (i.e. problems with attention, memory, and information processing), and a

movement disorder similar to Parkinson's disease (PD) (i.e. a disturbance of gait, loss of balance, dystonia, bradykinesia, and tremor) (Bowler et al., 2007).

Environmental studies of airborne Mn have been relatively rare and results of a select few studies have been published. At the first major conference on the effects of long-term, low-level exposure to Mn in Little Rock, Arkansas in 1997, an inter-disciplinary international forum was held on state of the art research data on this issue, which was followed by publication of the peer-reviewed papers presented at that time. In this special April/June 1999 issue of the Journal of NeuroToxicology only 7 out of 33 published papers reported on environmental human exposure to Mn, including exposure to Methylcyclopentadienyl Manganese Tricarbonyl (MMT) (2 publications) and the neuropsychological effects of environmental Mn exposure (5 publications). Lynam et al. (1999) reported no effects of MMT and of ambient air levels of car emissions in Toronto, Canada. Zayed et al. (1999) also reported a lack of effects of potential exposure to MMT in residents near a gas station and underground parking garage, but did report "substantial concentrations of respirable manganese ($Mn_R$)".

Neuropsychological effects of environmental Mn exposure were reported by Mergler et al. (1999) in their study of 273 community residents in Quebec, Canada, for whom a relationship of lower neuropsychological function with higher Mn in blood was found. Higher levels of Mn were also shown to be associated with changes in coordinated upper limb movements and poorer learning and recall. An interaction between Mn and increasing age (>50) was found for motor tasks. Bowler et al. (1999) reviewed the literature on neuropsychiatric effects of Mn on mood and described these effects in the group of 273 community residents in Quebec. These effects were categorized to be anxiety, psychotic experiences, emotional disturbance, fatigue, compulsive behaviors and aggression and hostility. Baldwin et al. (1999) described the bioindicators and exposure data of the Mergler et al. (1999) study and reported that Mn in air samples of total suspended particulate measured at 4 sites, amounted between 0.009 $\mu g/m^3$ and 0.035 $\mu g/m^3$. These levels of Mn in air are considerably lower than those in East Liverpool.

Studies by Lucchini et al. (2007) report an increased prevalence of parkinsonian disorders associated with Mn exposure in the vicinities of ferroalloy industries in Northern Italy. Concentrations of Mn in settled dust measured in 206 municipalities were significantly higher near and downwind from two of four industrial plants. Near one of the four plants studied, airborne concentration of Mn in total dust averaged 300+ 533 $\mu g/m^3$ (range 20-1600). The estimated range of ultrafine $PM_{2.5}$ particles in six locations, within a distance of about 2 km from plant B (Lucchini et al., 2003) were also measured outside the plants in 2001 and showed a geometric mean of 0.69 $\mu g/m^3$ (range 0.2-1.8). The respirable fraction of Mn was reported to be 25% to 90% of the total dust from the plants.

In 2007, Finkelstein and Jerrett (2007) re-visited the concerns over industrial Mn emissions and those due to combustion of gasoline MMT and investigated the association of PD and Mn exposure in 110,000 subjects from Toronto and Hamilton, Canada. They used residential postal codes and did geocoding to assign longitude and latitude coordinates for each resident. Thus, the residential locations were analyzed for distance from a major urban road. Hamilton residents were exposed to both mobile sources of Mn from MMT and industrial Mn emissions from steelmaking industry, while residents in Toronto were without "substantial"

industrial emissions of Mn. Manganese in total suspended particulate in Hamilton (TSP-Mn 50.5, to 92.1 ng/$m^3$ ) was found to be significantly higher than in Toronto (9 ng/$m^3$). Results of the prevalence curves for PD indicated that ambient exposure to Mn results in diagnoses of PD at an earlier age, which was postulated to be consistent with the theory that increased Mn exposure would be associated with increased neuronal loss in the aging process.

Although few comprehensive studies of environmental exposure to Mn have been reported, a small body of recent research has associated Mn exposure with learning and neuropsychological deficits in elementary school children. Wasserman et al. (2006) reported dose-effect relationship between concentration of Mn in drinking water and decreased IQ. Likewise, Chinese investigators reported that scores on tests of learning and neuropsychological functions were lower in elementary school children exposed to Mn in drinking water at levels of 241-346 ug/l than in children from a control group with very low Mn levels in drinking water. Levels of Mn in hair correlated with several neuropsychological scores. Additionally Zhang et al. (1995) reported lower levels of serum 5-hydroxytryptamine, dopamine, norepinephrine and acetylcholine esterase in the exposed children. Bouchard et al. (2007) reported a significant relation between levels of Mn in water and hair of children as well as an increase in indicators of hyperactive behaviors with Mn in hair.

In conclusion, although recent studies on children exposed to Mn- through drinking water show decrements in neuropsychological performance, none of the recent environmental studies on adults included a comprehensive neuropsychological test battery in the context of air measurements, such as those detailed in the East Liverpool air reports. Only the earlier work by Mergler et al. (1999) related Mn in air to neuropsychological function. This present study seeks to fill that gap and will utilize past knowledge gained from these studies by using a more refined and recently updated neuropsychological test battery, including the Computerized Adaptive Testing System (CATSYS) to assess hand tremor and body sway, in addition to geo-coded data in relation to the Mn air results already performed by ATSDR and EPA in East Liverpool, Ohio.

## BACKGROUND

Air monitoring at the three locations near the S.H. Bell Company in East Liverpool has already been conducted by the Ohio EPA and the ATSDR over a period of over 9 years. This proposed project is to be conducted with a randomly selected sample of adult residents aged 30-75 years (under a contract between SFSU and the US EPA with partial in-kind contributions of personnel from the ATSDR and EPA). Randomly selected study participants will include 100 residents, selected from a purchased list of addresses in East Liverpool, OH, within a perimeter of 2.5 miles from the Water Plant air monitor. This study will include neurological and neuropsychological evaluations and measures of Mn exposure in air and levels of Mn in biomarkers measured in blood, hair, and toenails. Upon completion, this study will contribute knowledge about the potential risk for health effects associated with the higher ambient Mn air measured in East Liverpool.

East Liverpool has 13,089 residents and is similar in size to the two towns (Marietta: 14,515 residents and Mt. Vernon: 14,375 residents) currently being studied by the investigators (see Appendix C). East Liverpool is also similar to these two towns in ethnic and gender

proportions, median age, and income; however, the percentage of residents living below poverty in East Liverpool is lower than in Marietta and Mt. Vernon. The percent of residents having less than a high school education in East Liverpool (26.6%) is higher than in Marietta (15.9%) and Mt. Vernon (19.8%) and fewer residents of East Liverpool are college graduates or have post-graduate degrees. Both Mn-exposed towns, Marietta and East Liverpool, are situated on the Ohio River and both have Mn polluting industries near the city. Both Marietta and East Liverpool have industrial plants with documented chemical emissions, with Mn being the pollutant of greatest concern. The exposed town of Marietta has an industrial complex with a ferroalloys facility, Eramet, being the main point source for Mn emissions. Modeled Mn air emissions in Marietta have been shown to range from 0.04 to 0.96 $\mu g/m^3$; while East Liverpool, the proposed more highly exposed town, has Mn-air concentrations ranging from 0.10-23.0 $\mu g/m^3$. Mn exposure for Mt. Vernon was considered to be low based on data from the Toxic Release Inventory, and the town was therefore selected as a comparison/control town.

**Study Design:** The proposed health study will utilize a cross-sectional design using a Mn-exposed group of 100 residents of East Liverpool drawn at random as an add-on to the 100 exposed residents from Marietta and 90 comparison residents from Mt. Vernon, who are part of a prior study currently being completed. As for the prior study, the same age group (30-75 years of age), and the same methods of selection/recruitment, inclusion and exclusion criteria, and neurological and neuropsychological test measures and procedures will be used in this current study of East Liverpool, Ohio. The prior study conducted in Marietta and Mt. Vernon, had received IRB approval from both SFSU and the Ohio Department of Health (ODH).

- **Data collection methods:** The same carefully controlled and standardized test administration instructions as those used in the Marietta/Mt Vernon study will be applied to the data collection procedures in East Liverpool. To the extent possible, the testers will be the same as in the prior study. The test battery and test description are listed in Appendix B. All non-copyrighted questionnaires are also submitted to the IRB for approval. Additionally, an IRB protocol will be submitted to the US EPA, who have contracted the University of North Carolina to conduct their IRB reviews.

The data collected in this study will include the following:

1. Air exposure of Mn, already collected by the EPA/ATSDR for the period between 1999 and 2009 (9 years and 8 months).
2. Neuropsychological (including mood and motor efficiency) tests (see Appendix B of the enclosed proposal).
3. Neurological function will be assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) administered by the same trained physician (2 subscales: Activities of Daily Living and Motor Function)
4. The CATSYS (Danish Product Development) – consisting of 4 postural sway conditions and hand tremor.

5. A health questionnaire containing sections on residency, symptoms, medical history, medications, work history and behaviors, diet, and personal demographic information (enclosed).
6. The possibility of worry impacting symptom reporting in the East Liverpool group will be addressed in two ways: A) we will include an Environmental Worry Scale (EWS, enclosed), scores of which will be analyzed as a potential confounder and B) all examiners will be (most already are) trained in detecting symptom and cognitive impairment exaggeration. Additionally, a short test of effort (Rey-15) will be administered, which if failed, will result in the administration of a highly regarded test of symptom validity, the Victoria Symptom Validity Test (VSVT). This test is designed to provide evidence that can confirm or disconfirm the validity of an examinee's cognitive and symptom impairments. In the event that the examinee fails both the Rey 15 and the VSVT, that participant's test scores will be excluded from the group analysis.
7. Whole blood will be analyzed for levels of manganese (Mn), mercury (Hg), cadmium (Cd), and lead (Pb) and serum will be used to evaluate ferritin and the liver enzymes, alanine-aminotransferase (ALT) and gamma-glutamyltransaminase (GGT). Toenail and hair samples will be analyzed for levels of Mn. In total, 12 mL whole blood will be collected from each participant for analyses. Whole blood samples will be shipped on dry ice by Fed Ex immediately to the CDC and serum samples to the U.S. EPA NHEERL Core laboratories. The samples will be identified by each participant's ID number only and no names will be included

The ATSDR, represented by Dr. Michelle Colledge, will be collaborators on the proposed project to assist on the analysis of the monitoring data from the East Liverpool region. Dr. Danelle Lobdell, an epidemiologist from the U.S. EPA National Health and Environmental Effects Research Laboratory, Human Studies Division, will serve as the Technical Consultant on the project. The data of Mn in air collected over the 9 years and 8 months and published in the November 2010 Health Consultation report, will be the basis for determining external Mn exposure. Additionally, internal Mn dose will be assessed through the analyses of Mn in blood, hair, and toenail analyses for the presence of Mn in the body. The study of the East Liverpool group will enable the comparison of the residents' neuropsychological test performance, motor efficiency, movement, and function on postural sway and hand tremor with that of the Marietta and Mt. Vernon groups and with established normative data. The information collected from the medical, social, and psychological history questionnaire will be used to control for factors (other than exposure to Mn) that could affect an individual's test performance. The use of standardized and well-recognized tests will also allow us to examine the neuropsychological test performance data in relation to the exposure data (both internal and external) to determine the presence of dose-dependent differences in neuropsychological function.

- **<u>NEUROPSYCHOLOGICAL TESTS AND DESCRIPTIONS</u>**
  The test battery and test descriptions are listed in Appendix B.

- **Data Analysis Plan**

In order to compare scores on neuropsychological, motor and mood tests, and the UPDRS between the three towns, the general linear model will be used. This will test for differences between participants in the three towns, including pairwise comparisons for differences in domains of neurological, neuropsychological, mood and motor functioning, with covariates included in the model as necessary. Logistic regressions will be used for dichotomous outcomes such as symptom and illness frequencies in each town, comparing the relative risk between the samples after controlling for the effects of covariates.

Multiple regression analyses will test for relationships between Mn levels in air, blood, hair, and toenails, and neuropsychological test scores in East Liverpool, and these relationships will be compared to the results recently obtained in Marietta. Logistic regressions will be used for categorical outcomes to examine the relationship between Mn levels in air and risk for particular illnesses or symptoms and mood.

Power analyses using G*Power statistical software indicated adequate statistical sensitivity with a sample size of 100. Setting power at 0.80 and alpha at 0.05, one-way between groups analyses of means would be powered to detect an effect size of f=0.18 or greater. This is halfway between a small and medium effect size based on Cohen's (1988) guidelines, and should be sufficiently sensitive to detect the effects of manganese exposure in this sample, based on theory and previous research.

- **Limitations of the available Exposure Estimates**

The current proposal does not include individual quantitative estimates of actual air Mn exposures but the monthly averages of Mn in air monitored in the area studied will be used to model exposure. Questionnaires and biomarker results will be used to help rule out confounding exposure from other chemicals analyzed in blood and from effect modifiers measured in serum. The understanding is that the current proposal's "exposure assessment" includes only one group of East Liverpool participants residing within 2.5 miles of the Water Plant air monitor who have on average about 10 x greater airborne Mn exposure than residents in Marietta. The basis for this exposure assumption is described above. Dietary information of foods containing Mn, Mn in diet supplements, and Mn in blood, hair, and toenails will be collected and analyzed with the functional variables assessing possible dose-effects. This study is supplemental to the pilot study for the larger proposed ATSDR study and has a narrow focus on neurobehavioral and health outcomes in relation to Mn in ambient air, blood, hair, and toenails, with diet as an additional surrogate for Mn.

- **Significance:**

1. This study will contribute to the knowledge of effects of environmental exposure at different levels to airborne Mn on neurological and neuropsychological functions of randomly selected adults.
2. Although Mn exposure has been reported in numerous studies of occupational workers, very few reports of environmental Mn exposure are available. This study will add to the findings of the Marietta study by investigating a much higher exposed town, which will contribute to

- knowledge about environmental Mn data in air and in blood, hair, and toenails, and the level of exposure that may be related to developing symptoms associated with Mn exposure
- knowledge of the relationship of Mn in air to neurological, neuropsychological, and health status
- addressing concerns about potential health effects in the exposed town of East Liverpool when comparing the adult test data to that of Marietta and Mt. Vernon and to normative ranges of unexposed populations
- piloting and refining the study methodology for a larger study being planned by the ATSDR

## 2. PARTICIPANT POPULATION

**a. Participants:** The proposed health study will recruit 110 individuals (10 will be alternates if there are cancellations) residing within 2.5 miles of the Water Plant air monitor in East Liverpool, Ohio. Due to the demographic similarities between East Liverpool and the two communities already studied, the selected participants are expected to be similar on age, gender, ethnicity, and level of education (Appendix C).

**b. Inclusion criteria**

To be included in the study, participants must be 30-75 years old and have 10 years or more of residency in East Liverpool. Participants must live in homes serviced by the municipal water supply and must reside within 2.5 miles of the Water Plant air monitor in East Liverpool, Ohio.

**c. Exclusion criteria**

1. having had a major occupational exposure to pesticides, fungicides, or herbicides, carbon monoxide (CO), or other heavy metals requiring a medical visit,

2. a diagnosis of a psychiatric, neurological, or hepatic medical condition, including: stroke, electroconvulsive treatment, epilepsy, brain surgery, encephalitis, meningitis, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's dementia, schizophrenia, bipolar disorder,

3. current treatment for alcohol or drug dependence,

4. prior head injury or a stroke resulting in hospitalization for more than 1 day,

5. having worked at S.H. Bell or Eramet Marietta Inc. at any time,

6. women who are pregnant or nursing.

**RECRUITMENT**

Participant recruitment will be preceded by public announcements of the study. The recruitment plan is outlined below.

**a) Community Meetings and Health Study Announcements**

1. Community meeting announcements will be made via radio, newspaper, and television.
2. The study P.I. and her assistant will travel to East Liverpool on September 14th, 2011 to meet with the Health Commissioner and her board, on September 15, 2011, presenting the study. The same evening, a meeting for the community will be held to describe the study as outlined below in # 3 open to the residents and other interested parties of East Liverpool.
3. The community meeting in East Liverpool will consist of a presentation of a brief slide show, previously presented at the Marietta, Ohio community meeting but revised for East Liverpool. Around the time of the community meeting, invitation letters will be mailed to all residents within a 1 mile radius of the Water Tower monitor and to a random sample of approximately 1/3 East Liverpool households within the 1-2.5 mile area, selected at random form a purchased list of postal addresses. The letter will describe the East Liverpool Community Health Study and its procedures. The letters will also contain a stamped, self-addressed postcard where residents will be able to indicate their interest in study participation if they are eligible (determined by a phone call interview after the cards are received in the research office).

**b) Recruitment Procedure:**

1. The sample of households in the area of 2.5 miles surrounding the East Liverpool Water Plant air monitor and S.H. Bell will be obtained from the 911 database, and a purchased list of all complete postal addresses.
2. Letters will be mailed to all residents within the 1 mile area from the Water Plant air monitor and a randomly selected group of addresses representing 1/3 of the database containing the postal addresses for the 1-2.5 mile area. The letters will contain a self-addressed, stamped card which could be used to indicate willingness to participate or denial to participate in the health study. If participants indicated interest, a brief questionnaire listing the exclusion factors will be administered during subsequent telephone calls to the participants. If the number of return cards received 2 weeks after the mail out is insufficient, the research team will attempt to contact potential participants via telephone. In an attempt to reach potential participants, a maximum of three phone calls will be made to those who have an answering machine and a maximum of five phone calls for those who do not have an answering machine. The telephone numbers will be obtained from an East Liverpool telephone book or the white pages. If the responses are insufficient in number, this process will be repeated until 110 adults are available to be tested or until the maximum number of phone calls has been

reached for each potential participant (10 alternates are included to be called if any of the first 100 participants cannot come in the last few days prior to the appointment).

3. Calls will be made until 110 individuals agree to participate.
4. Selected participants will be contacted by telephone 4 weeks prior to the study to set up appointments at a convenient location.
5. Two days prior to the appointment, telephone appointment reminder calls will be made.
6. Because of concern and interest about chemical exposure, a relatively high response rate of ~50% is expected in East Liverpool.

**STUDY PROCEDURES**

**1.** The above recruitment methods will be followed.

**2.** Examiners will meet the day prior to testing and set up testing areas, review all test administrations and set up stations and offices where consent forms, interviews, and tests will be administered.

**3.** At the time the study will begin, scheduled study participants in groups (three groups per day) of 11 people (+ 1 extra person on one of the days) will be seated in a common area and greeted by the P.I. who will give a brief introduction about the study, the procedures, and the consent form.

**4.** The P.I. will interview all of the participants with a brief, somewhat structured interview schedule, asking participants about special concerns, fears and observations related to their exposure. The check-out staff person will at this time collect and de-identify the participant's list of current medications, (copied each night at the conclusions of testing) which will be hand-carried in carry-on luggage by the P.I.

**5.** Trained examiners will introduce themselves to participants and will explain the consent form in detail. Participants will be given time to ask questions. Then two copies of the informed consent will be signed; one for the participant and one for the researcher.

**6.** The participant will be invited to accompany one of the testers to a private room for testing. The neuropsychological testing will be conducted without any identifiers on the test protocols other than the respective I.D. number. Examiners will be two neuropsychologists and six graduate students in psychology, who will be trained by the P.I. and senior staff (all have completed the course for the protection of human subjects – certificates enclosed).

**7.** After completion of the tests, the study staff will introduce participants to the certified phlebotomist, who will draw a total of 12 mL of venous blood from each participant for analysis. The Centers for Disease Control and Prevention (CDC) Environmental Health Laboratory has agreed to perform the blood analyses of whole blood for Mn, Pb, Cd, and Hg levels. Ferritin levels, and ALT and GGT activities in serum will be determined by the U.S. EPA NHEERL Core laboratories. A total of 200 samples (two vials per participant, 6 mL each) of whole blood will be collected from study participants by the licensed and trained phlebotomist/medical technician. Presumably, one needle stick per participant

(or as few as needed) will be used by the certified phlebotomist/medical technician. Four mL of whole blood will then be centrifuged at 800 x g for 10 min at room temperature to separate the serum. Whole blood will be kept at 4°C and serum samples will be immediately stored at -18°C until analysis and sent weekly by Express Mail to the laboratory. Half a milliliter of serum is needed for the analysis of ferritin concentrations by immunoturbidity using the Roche Tina-quant assay on the Hitachi 912 clinical analyzer. Also half a milliliter of serum is needed to analyse the activities of the liver enzymes ALT and GGT with a Beckman Synchron LX20 using an enzymic rate method. The usual QA/QC methods of the CDC Laboratory will be applied. Each analytic run is surrounded by at least two levels of bench quality control and one blind quality control sample is inserted with each run (40-60 samples). The methods are CLIA-certified and multiple PT are run, as available. The DLS QA/QC system (Caudill et al., 2008) is referred to as the Multi-Rule Quality Control System (MRQCS). The CDC rules are similar in nomenclature to Westgard's format, but the rules are not identical. Some of the additional features of MRQCS include the ability to distinguish between within-run and among-run precision, accommodating variable numbers of QC measurements per run and accommodating variable numbers of QC samples per pool. Quality control measures include analysis of initial calibration verification standard (National Institute of Standard and Technology standard reference material (NIST SRM) 1643e (trace elements in water, Gaithersburg, MD), a solution of NIST traceable 1 ng $ml^{-1}$ manganese standard as the continuous calibration verification standard, procedural blank and Certified Reference material GBW 07601 (human hair) (Institute of Geophysical and Geochemical Exploration, Langfang, China) will be used as the quality control sample. Results will be given as the average of five replicate measurements of the instrument. Recovery of the analysis of QC standard by this procedure is 90% -110% and, precision is given as %RSD (SD*100/Mean) and for hair samples it varied from 1%-25%.

8. Hair samples will be collected using the following procedures: The collector will first evaluate the presence of sufficient hair on head for collection. Approx. 1-3 cm of hair should be available for collection. The scissors will be cleaned with an alcohol swab in front of the participant. Hair will be cut as close to the skull as possible from the base of the skull near the point halfway between the spine & ear (lower right or left quadrant). When enough mass is an issue, typically on men, smaller snips of hair will be taken in a random pattern. The side of hair sample that was close to the scalp will be marked by tying that end off with sewing thread and the collected hair will be placed into a small plastic bag with the participant's id clearly indicated on the bag. All small bags will be sealed and placed into a container and sent to the laboratory for analysis.
9. Toenail samples will be collected in the following manner: A pair of titanium dioxide nail clippers will be rubbed with alcohol swabs to be thoroughly cleaned between people. Participants will be asked to clip their nails from all ten toes onto a clean paper (to make it easier to catch all the clippings) and place the collected nails in a small plastic bag labeled with their respective ID. All small bags will be placed into a container and send to the laboratory for analysis.

Whole sample (Hair/Toenails) will be pre-cleaned with 1% Triton X-100 solution prior to analysis to remove extraneous contaminants. Samples will be acid digested using ultra pure nitric acid at room temperature for 24 hours. Diluted samples will be analyzed for manganese using inductively coupled plasma mass spectrometry (ICP-MS, DRC-II, Perkin Elmer, Norwark, CT) using indium as the internal standard.

**10.** Two post-baccalaureate level students who were also part of the testing team in Marietta and Mt. Vernon, OH, will conduct check-in and check-out and review the questionnaires and individual participant folders to ascertain that all tests have been completed before the participant leaves. This protocol completeness review will be performed in order to detect unintentional omissions. Participants will at no time be pressured to answer any items they choose not to answer.

**11.** Upon completion of the study, a gift card for $50.00 for a local store will be presented to each participant as a token of appreciation for participation in the study.

**12.** Feedback of the group's results will be given to the community and all interested parties either in person or in written form during late summer of 2012. If additional funding becomes available, the P.I. will also present group results of the study in a community meeting in East Liverpool.

**13.** After the conclusion of the study, a brief feedback report will be prepared and mailed to each participant reporting the individual's test scores (by domain of function) and results of biomarker analyses. This report will also indicate whether the test results were:

a) within the normal range
b) of concern, needing a referral to the family physician for further assessment by specialists as indicated.

**14.** All relevant professional parties and city officials will be contacted and given feedback of the group's findings.

**15.** All inquiries by the media will be answered by the team of investigators including the P.I., Mr. Greg Stein from ODH and Dr. George Bollweg, representing the Regional U.S. EPA. Prior to any release of data, results and talking points will have been presented to the entire group of investigators, collaborators and advisory board for input and final wording.

**Research details**

- The proposed study will take place in rented facilities at locations convenient for participants in East Liverpool, Ohio (the Motor Lodge hotel). The P.I. has made sure that they offer the privacy needed for conducting the study procedures.
- Each participant will be engaged in the study procedures for an average of 2.5 to 4.0 hours.
- It is expected that the brief introduction to the study by the P.I. and consent procedure will take no longer than 10 minutes since participants will already have received detailed information in the recruitment letters. Participants will be engaged in filling out

questionnaires for approximately 50 minutes, following which they will have a brief interview by the P.I. for about 10 minutes. The administration of the neuropsychological test battery is expected to take approximately 90 minutes. The administration of the CATSYS is expected to take 10 minutes. The neurological examination (UPDRS) will last 15 minutes. Participants will then have refreshments for about 10 minutes before being introduced to the certified phlebotomist for the drawing of the blood and hair sample collection, followed by the collection of toenail clippings by participants, which will each take 10 minutes.

**4. RESEARCH RISKS**

- Drawing venous blood from the arm may cause minimal pain when the needle is inserted. There is also a slight risk of bruising and infection where the needle punctures the skin. In rare cases, some people may experience lightheadedness, nausea, or fainting. The certified phlebotomist is trained in recognizing and dealing with these types of reactions. All possible accommodations will be made should this occur. Cutting a small amount of hair will be done with a blunted scissors which will prevent any accidental injuries. Blood samples will also be marked with an ID number only to ensure those analyzing the blood/serum are blinded to the identity of the participant. Arrangements will be made with a local physician on call, who will be recruited by a local colleague practicing in East Liverpool. The pager number and location of this local physician will be obtained so he/she may be contacted and available to address any medical emergency that may arise. Although such emergencies are highly unlikely, a participant, if necessary can be brought to the nearest Emergency Room at the local hospital.
- There is a risk of experiencing slight fatigue during testing. Testers are trained to look for signs of fatigue and a break will promptly be offered. The participants will also be informed that they can take a break or discontinue testing at any point.
- Participation may involve potential loss of privacy. To minimize this, results will be stored in a password-protected computer database with no identifying information attached. Hard copy files of all of the data will be kept by the P.I. in a locked file cabinet for 5 years with documents containing ID numbers only. Any documents or computer files linking ID numbers to names will be kept in a separate, locked file cabinet (or computer database) only accessible by the P.I. and will also be destroyed after 5 years.

**5. CONFIDENTIALITY**

All test results will be linked to an ID number, with all personally identifying participant information removed. Results will be stored in an encrypted document on a password-protected computer and all paper materials will be stored in a locked file cabinet in Dr. Bowler's research office laboratory at 8371 Kent Drive, El Cerrito, CA 94530. Only Dr. Bowler will have access to information linking ID numbers and the identities of the participants. Each page in the participant's folder will be coded with an ID number only.

Security will be maintained by having an alarm system in the building and by having each staff member sign a special Data Contract to maintain confidentiality of the data, refraining from any public conversations about the participants. The data will not be released unless subpoenaed by a court of law. Anyone working on the data will also be required to sign this, guaranteeing confidentiality and guaranteeing that these data will not be used unless the P.I. is involved in order to guarantee privacy to the information given by the participant. All data will be maintained for approximately 5 years in hard copy, limiting access to only authorized individuals. The electronic data will be securely stored indefinitely. Unauthorized access will be reported to the relevant parties (IRB, participants, stakeholders). Electronic data will be saved on a device that has the appropriate security safeguards, such as unique identification of authorized users, password protection, automated operating system patch (bug fix) management, anti-virus controls, firewall configuration, and scheduled and automatic backups to protect against data loss.

**6. BENEFITS**

Participants will receive the test results in writing, which they can send to their physician. We will indicate whether any results are of concern. If abnormalities are found, they will be referred to your family physician.

**7. PAYMENT**

Upon completion of the study, a gift card for $50.00 from a local store will be presented to each participant as a token of appreciation for participation in the study.

**8. COSTS**

There is no cost for taking part in the study, aside from the transportation costs of coming to the appointment. Transportation costs involved in coming to the facility, which will be selected to be convenient for participants, will not be reimbursed. The researchers, research team and sponsors of this project will not provide medical care nor cover the cost of medical care for participants.

**9. ALTERNATIVES**

The alternative is not to participate in the research.

**10. CONSENT/ASSENT PROCESS AND DOCUMENTATION OF CONSENT**

**a.** The study will first be introduced to East Liverpool residents at the community meeting that will take place in September 2011. A slide show detailing the study procedures for the community residents will be presented. Residents will be informed that they might receive a letter from the P.I. containing the study description. If selected, residents will be asked to complete and return a stamped, self-addressed card indicating willingness or non-willingness to participate to the P.I. Participants will be able to have their questions answered during the recruitment and screening calls, as well as later, at the time of the appointment. They will be able to ask the P.I. any additional questions that may arise either on site after the meeting or over the telephone when they are administered the inclusion/exclusion questionnaire. They

also will be provided additional time to ask questions when the IRB approved consent forms are explained and reviewed by the examiners with each participant at the time of testing. The consent forms will be kept in each participant's testing protocol folder for the duration of the study procedure. Upon arrival at the P.I.'s office, the consent forms will be removed from the folders containing the participants' test protocols and will be in possession of the P.I. , along with the list connecting IDs and names. These forms will be kept in a locked file cabinet in the P.I.'s office.

**b.** Participants will receive a signed copy of the consent form.

**11. <u>INVESTIGATORS' QUALIFICATIONS</u>**

All investigators and trained examiners/psychometricians hold valid NIH Ethics Certificates and will follow the usual confidentiality rules. They will not have names of the participants on their protocol they may score and review. The following are the team of experts conducting the study:

a. **Professor Rosemarie Bowler** is a licensed neuropsychologist, qualified medical evaluator, and an emerita lecturer at SFSU. She has published numerous research articles on neurotoxicants and their effects on health. She has previously been on the committee at the National Academy of Science, Institute of Medicine and has served on the CDC/ATSDR Board of Scientific Counselors. She has taught at SFSU since 1977, recently retired, but is still teaching, training and supervising SFSU Psychology graduate students, as well as Ph.D. students in other universities. Professor Bowler has conducted numerous studies of neurotoxicity in adults and has also been responsible for 5 major epidemiologic studies of the effect of neurotoxicants on children (in California, Ohio, France and New Mexico). She has served on numerous committees and boards regarding the chemical effects of exposures on human populations.

**Dr. Danelle Lobdell**, an epidemiologist from the USEPA at Chapel Hill, NC, is the technical advisor on the project. She will give input on aspects of exposure, selection, statistical analyses and general communications with the community, federal, state and local agencies, and community and scientific presentations. She will be a co-author on manuscripts.

**Dr. Harry Roels,** Université catholique de Louvain (UCL), Brussels, Belgium. Professor Roels has a long history of scientific work with human populations exposed to neurotoxicants. Professor Roels is one of the most well-known scientific experts on Mn, in fact his study of battery workers in Belgium resulted in the lowering of the Threshold Limit Values (TLVs) of Mn. Dr. Roels is a sought out international expert on Mn and is on many international federal committees on scientific issues related to Mn. He will work closely with the P.I. on all neurotoxicologic and epidemiologic areas of the study and be a co-author on all manuscripts.

**Dr. Michelle Colledge,** Environmental Health scientist, Division of Regional Operations for Region 5 of the US EPA and ATSDR, conducted the health consultation detailing Mn exposure in EL for almost 9 years. She authored the East Liverpool Air Quality Report, November 16, 2010.

Dr. Colledge will assist the P.I. and Dr. Roels on all aspects of selection of the area to be studied, air exposures, the design of analyses using the air data and the analyses of potential relationships between the neurological, neuropsychological and health data and Mn exposure. She will be a co-author on all papers.

**Dr. Yangho Kim**-Department of Occupational and Environmental Medicine, Ulsan University Hospital, College of Medicine, South Korea. Dr. Kim has previously conducted the neurological examinations using the UPDRS in the Marietta and Mt. Vernon studies and has submitted a manuscript on these findings. He will again administer the UPDRS to all participants in EL and likely will author manuscripts with the research team on the results of the neurological function in EL, comparing the results to normative data and to the data collected from his examinations of residents in Marietta, OH and Mt. Vernon, OH.

**Dr. George Bollweg**, US EPA Region 5, environmental health scientist, will assist the P.I. and study team on issues of exposure to Mn and other substances. He is a collaborator and will give input on all issues related to Mn exposure in air and biomarkers. He will be a co-author on manuscripts and facilitate communication with the public and the Region.

**Mr. Greg Stein,** (ODH), community involvement and health education co-ordinator, will assist the P.I. with community involvement and communications and media related activities. He will assist with the production of media materials and community friendly fact sheets announcing the study, giving results and feedback of the study and also will assist with the health effects results of the study and communication to participants and stake holders. He will be co-author on manuscripts describing the overall study, methods and results.

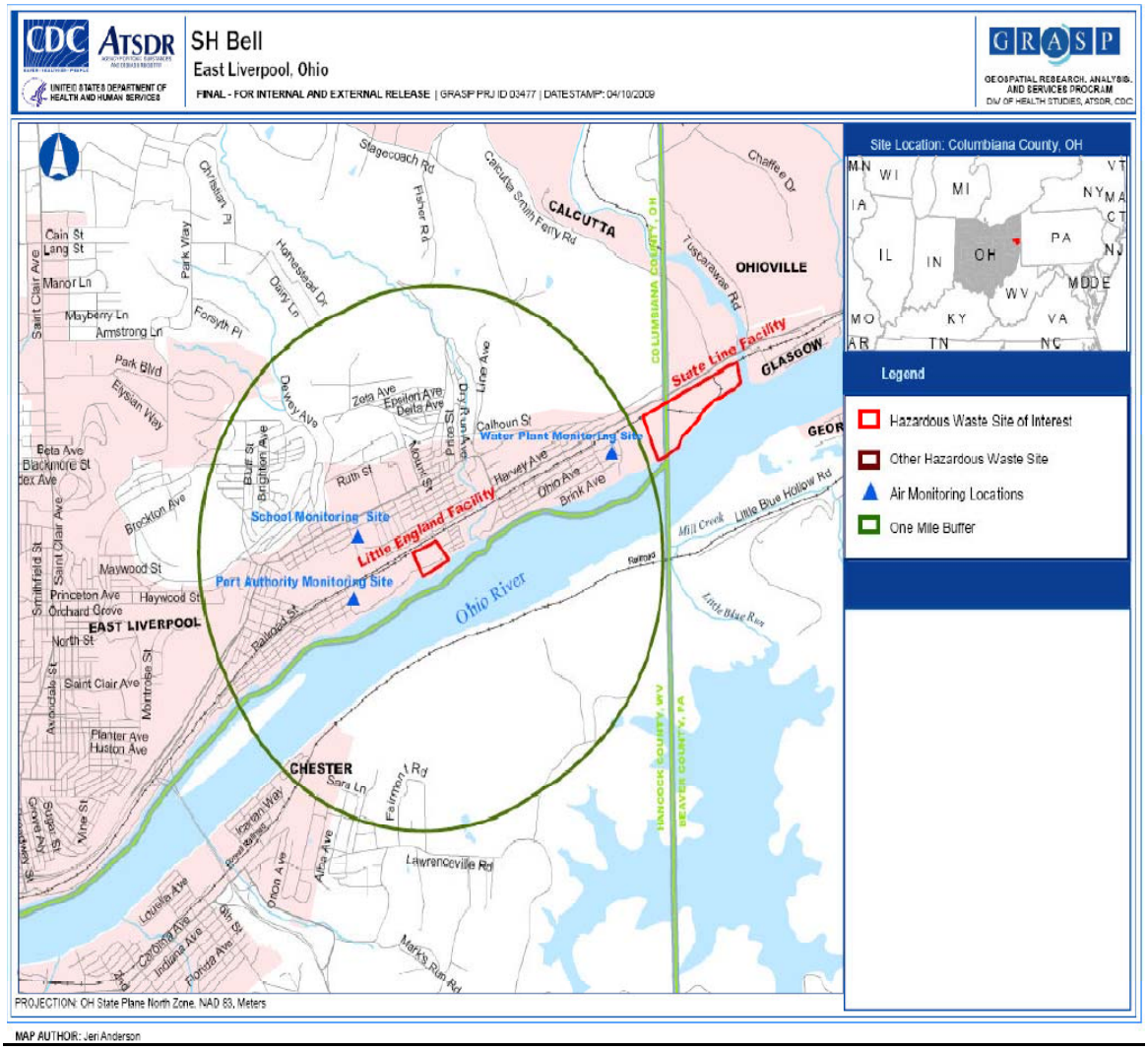
**Trained examiners/psychometricians:**
**Vihra Gocheva, MA** (pending, San Francisco State University)
**Matthew Harris, MA, Ph.D.** (pending, Alliant International University)
**Linda Mora, Ph.D.,** Oakland Children's Hospital
**Katherine Wilson, MA, Ph.D.** (pending, Alliant International University)
**Beth Stutzman, MA, Psy.D.** (pending, The Wright Institute)
**Matthew Beristianos, MA, Ph.D.** (pending, Alliant International University)
**Katherine Brown, Psy.D.** (pending, Alliant International University)
**CATSYS administrator - Ralph Rasalan, MA** (pending, San Francisco State University)
2 trained psychology students-TBA
1-2 additional trained data-entry persons from psychology research classes at SFSU

## 12. FUNDING SOURCES

Funding by the USEPA is awarded as a contract from July 20, 2011 to July 19, 2011. The study will commence immediately once final approval is given, and testing will take place on November 3, 4, 5, and 6, 2011. The main contact person responsible for communication of the cooperative at the U.S. EPA is Dr. Edward Hudgens from the U.S. EPA. Dr. Danelle Lobdell is the technical advisor at the National Health and Environmental Effects Research Laboratory in

Chapel Hill, NC. The contact person for EPA at Region 5 is Dr. George Bollweg. Funds will be processed through the Office of Research and Sponsored Programs (ORSP) at SFSU. No conflict of interest exists for any of the researchers.

## Appendix A. East Liverpool Area Map in Relation to the 3 Air Monitor Sites



## Appendix B. East Liverpool Test Battery

### I. NEUROPSYCHOLOGICAL BATTERY (120 MIN)

A. Cognitive (90 min):

1. Animal Naming
2. Digit Symbol Coding
3. Rey-O Copy
4. Digit Span
5. Rey-O Immediate
6. ACT
7. Stroop Color Word Test
8. Trails A & B
9. Similarities
10. Rey-O delayed
11. NAB Memory
12. REY-15
13. Victoria Symptom Validity (if needed, based on Rey-15 scores)

B. Motor & Tremor :

- CATSYS
- Grooved Pegboard
- Fingertapping
- Dynamometer
- Parallel lines

C. UPDRS – ADL and Motor (15 minutes)

D. Mood:

- SCL 90-R
- BRFSS
- Satisfaction with life Scale
- Environmental Worry Scale (EWS)

### II. SELF-REPORT QUESTIONNAIRES

- Health Questionnaire

### III. BIOMARKERS & AIR MEASUREMENTS

A. Blood:

- Mn, Pb, Hg, Cd

B. Hair
   Mn

C. Toenails:
   - Mn -10 toenail clippings

D. Serum:
   - Ferritin

**Test Battery Details**

**Cognitive Tests** *(In alphabetical order)*

***Animal Naming*** (Lezak et al., 2004)*:*

A category fluency test, requiring the naming of as many animals as possible in 1 minute.

***Auditory Consonant Trigrams (ACT)*** (Lezak et al., 2004):

A test of divided attention and concentration in which participants are orally presented with 3 consonant letters and a specified number from which they are asked to count backwards by three for 3, 9, or 18 seconds, at which point counting is interrupted and they have to recall the 3 consonants.

***Neuropsychological Assessment Battery (NAB): Memory Module*** (Stern and White, 2003):

A test with high ecological validity consisting of an array of subtests assessing learning and memory. Subtests include: list learning, shape learning, story learning and daily living memory with immediate and delayed recognition trials and forced-choice recognition.

***Rey-Osterrieth Complex Figure Test*** (Meyers and Meyers, 1995)*:*

Assesses planning, organizational skills and problem-solving strategies and perceptual, motor and memory functions. To assess visuospatial constructional ability and visuospatial memory participants are asked to copy a complex figure and then to reproduce it after a 3 and 30 minute delay. It has been shown sensitive in Parkinson's disease and frontal lobe damage.

***Stroop Color and Word Test*** (Golden, 1978)*:*

Measures the ease with which a person can shift his/her perceptual set to conform to changing demands and suppress a habitual response in favor of an unusual one. The test involves word reading, color naming, and set shifting (reading color names printed in a different color ink) and is sensitive to dementia, depression, PD, schizophrenia, Huntigton's disease, and head injury. Color-blind subjects are excluded.

***Trail Making Tests (TMT)*** (Strauss et al., 2006)*:*

Tests of speed of attention, sequencing, mental flexibility, visual search and motor function. It requires connecting in order encircled numbers or letters, randomly arranged on a page. Part A requires the connection of numbers in order, and part *B r*equires the sequencing of numbers and letters in alternating ascending order.

***Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Subtests*** *(Wechsler, 1997)*:

***Digit Span (3 min) –*** a measure of attention and sustaining concentration

***Digit Symbol (3 min) –*** a spatial measure involving learning and speed

***Similarities* (*10 min*)** – higher level verbal abstraction and reasoning, will also be used as an estimate of premorbid function

**Mood and Health Questionnaires**

***Environmental Worry Scale (EWS)*** (Bowler and Schwarzer, 1991)

This scale is a 17-item measure developed to predict intention to avoid chemicals and has satisfactory psychometric properties. A 5-item version was used in this study to examine participants' particular concerns about chemical exposures, which is also has satisfactory normative properties.

***Health-Related Quality of Life Scale (BRFSS)***(Centers for Disease Control and Prevention)

This scale is a brief 4-item scale developed by the Centers for Disease Control and Prevention to assess self-perceived recent health, recent mental health and activity limitations. Nationwide normative data is available.

***Satisfaction with Life Scale*** (Diener et al., 1985)

This 5-item scale is a brief measure of life satisfaction. It asks participants to compare the current status of their life to their self-defined expectations of how they would like their lives to be. It has satisfactory psychometric properties.

***Symptom Checklist-90-Revised (SCL-90-R)*** (Derogatis, 1992)

A 90-item standardized scale asking participants to rate how much of a problem certain symptoms had been in the prior week, using a five-point scale. Domains/scales are: Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, Psychoticism, and summary indices.

***General Health questionnaire:***

A health questionnaire will be administered in a printed format. It will include socio-demographic information, smoking and drinking habits, hobbies with exposure to neurotoxic substances (gardening using pesticides, solvents, painting, welding etc), a history of illnesses and familial illnesses (with emphasis on neurological disorders), accidents and current symptoms (sleep, respiratory, cardiovascular, musculo-skeletal, neurologic and neuropsychiatric).

**Tests of Effort**

***Victoria Symptom Validity Test (VSVT)*** *(Slick et al., 2005)*

This computerized test is used to assess effort on memory tests and memory complaints exaggeration. The VSVT includes the presentation of 48 five-digit numbers and the forced-choice delayed identification of that number. Protocols where the number of correct items is above chance (50%) are considered valid. (15 minutes).

***Rey's 15-Item Visual Memory Test*** (Strauss et al., 2006)

It consists of a card with 15 printed items (letters, numbers and shapes) arranged in 3 columns and 5 rows. The examinee is told there are 15 different (emphasized) items to remember which are to be reproduced immediately on a blank sheet of paper following a 10-second exposure to the stimulus card. Although it is presented as a difficult task, it is actually quite simple because there is redundancy among items that reduces the amount

of information to be remembered (i.e. three main ideas). It is used to test motivation and potential deficit exaggeration.

**Neurological examination**

The motor/movement components and activities of daily living of the Unified Parkinson's disease Rating Scale (UPDRS) will be administered. The UPDRS is the most widely used scale for evaluation of clinical impairment in motor function. It contains 27 items, including assessments of posture, gait, postural stability, bradykinesia, and general hand and leg movements and tremor. It has good reliability and validity, utilizing the standardized test methodology and videotaped reference guide developed by (Goetz et al., 2003). It includes the Activities of Daily Living section (UPDRS II) and has 13 items of speech and daily activities and tasks. All items are rated on a scale of 0 (normal) to 3 or 4, depending on the scale with clinical descriptor for each rating ranging from normal to severe.

**Movement, Motor and Tremor** *(In alphabetical order)*

**Computerized Adaptive Testing System** (Danish Product Development, 1996)

1) **CATSYS hand tremo**r test. Hand tremor will be measured using the TREMOR 7.0 Test System. Vibrations within each hand are recorded with the TREMOR PEN. A two-axis micro-accelerometer is embedded within the tip of the 12 cm x 0.8 cm TREMOR PEN, which is connected to a PC data log system. The TREMOR PEN is sensitive to vibrations that occur in a plane perpendicular to the PEN axis. Vibrations will be analyzed using the Fourier Power Spectrum, which plots the normalized power distribution (the relative harmonic contents) of the vibration measurement period in a frequency domain. The Harmonic Index, highly sensitive to abnormal tremor patterns, relates the Fourier Power Spectrum to that of a single harmonic oscillation.
2) **CATSYS postural sway** test. This test of postural stability will be performed in three conditions (35 seconds in each condition) while the participant stands on a 50 cm platform balance plate with a) eyes open , b) eyes closed, and c) eyes closed standing on 2 cm foam. Postural stability is measured in Mean Sway (mean of force center position to all recorded center positions), Transversal Sway (sway movement from side to side), and Sagittal Sway (sway movement back and forth). A Sway Index (in relation to normative age-adjusted data) is computed for each condition.

***Fingertapping Test*** (Lezak et al., 2004)

A measure of bilateral psychomotor speed; The participant is asked to tap a lever as quickly as possible. Scores are the mean of five 10-second trials for each hand.

***Grip Strength*** *(Dynamometer)* (Lezak et al., 2004)

A test of grip strength with two trials administered bilaterally.

***Grooved Pegboard Test***(Lezak et al., 2004)

Tactile speed and visuomotor coordination; Pegs are inserted in the slots as quickly as possible; pegs have a ridge on one side, requiring a rotation to line them up with the slots. Completion time is recorded for each hand.

***Parallel Lines - Graphomotor Tremo****r*(Lezak et al., 2004)

Graphomotor tremor will be assessed by drawing lines as straight as possible within defined 3-inch and 1-inch high boundaries without lifting the pencil from the paper. Qualitative evaluation of tremor by a neuropsychologist with ratings of within normal limits, mild, moderate, or severe.

## Appendix C. 2000 US Census Demographic Factors

| | | East Liverpool | % | Marietta | % | Mount Vernon | % |
|---|---|---|---|---|---|---|---|
| NO. TOTAL POPULATION | | 13,089 | | 14,515 | -- | 14,375 | -- |
| PLACE OF BIRTH | % US-BORN (UB) | -- | 99.1 | -- | 98.8 | -- | 98.4 |
| | % OH-BORN (OF UB) | -- | 74.2 | -- | 66.7 | -- | 81.5 |
| | % FOREIGN-BORN (FB) | -- | 0.5 | -- | 1.2 | -- | 1.6 |
| | % NON-CITIZEN (OF FB) | -- | | -- | 43.2 | -- | 40.7 |
| POVERTY | % BELOW POVERTY | -- | 12.4 | -- | 16.9 | -- | 15.6 |
| RACE | NO. WHITE | 12,153 | 92.8 | 13,979 | 96.3 | 13,895 | 96.7 |
| | NO. BLACK | 630 | 4.8 | 157 | 1.1 | 166 | 1.2 |
| | NO. OTHER | 306 | 2.3 | 379 | 2.6 | 314 | 2.1 |
| ETHNICITY | NO. HISPANIC | 94 | 0.7 | 114 | 0.8 | 125 | 0.9 |
| SEX | NO. MALE | 6,070 | 46.4 | 6,757 | 46.6 | 6656 | 46.3 |
| | NO. FEMALE | 7,019 | 53.6 | 7,758 | 53.4 | 7,719 | 53.7 |
| AGE | MEDIAN AGE, YEARS | 35.7 | | 38.4 | -- | 37.1 | -- |
| | MEDIAN AGE MALE | | | 36.1 | -- | 33.9 | -- |
| | MEDIAN AGE FEMALE | | | 40.4 | -- | 40.0 | -- |
| | NO. 65+ YEARS | 2,100 | 16 | 2,573 | 17.7 | | 18.3 |
| | NO. FEMALE 15-45 YEARS (% ♀) | | | 3,330 | 42.9 | 3,051 | 39.5 |
| | NO. PRE-SCHOOL ≤ 5 YEARS | | | 947 | 6.5 | 1,171 | 8.1 |
| | NO. SCHOOL AGE 6-18 YEARS | | | 2,400 | 16.5 | 2,429 | 16.9 |
| | NO. 7-8 YEARS | | | 351 | -- | 406 | -- |
| | NO. 9-10 YEARS | | | 325 | -- | 370 | -- |
| | NO. 35-65 YEARS | | | 5,412 | -- | 5,075 | -- |
| | NO. 25+ YEARS | | | 9,381 | 64.6 | 9,504 | 66.1 |
| EDUCATION (FOR 25+ YRS) | % LESS THAN HIGH SCHOOL | -- | 26.6 | -- | 15.9 | -- | 19.8 |
| | % HIGH SCHOOL | -- | 45 | -- | 34.9 | -- | 39.5 |
| | % SOME COLLEGE | -- | 21.2 | -- | 25.9 | -- | 22.6 |
| | % COLLEGE | -- | 2.7 | -- | 12.8 | -- | 10.9 |
| | % MORE THAN COLLEGE | -- | | -- | 10.4 | -- | 7.2 |
| NO. HOUSING UNITS (HU) | | 5,728 | -- | 6,609 | -- | 6,713 | -- |
| | NO. URBAN | | | 6,426 | 97.2 | 6,543 | 97.5 |
| | NO. RURAL | | | 183 | 2.8 | 170 | 2.5 |
| | % BUILT BEFORE 1970 | | | -- | 75.5 | -- | 75.0 |
| | MEDIAN YEAR BUILT | | | 1948 | -- | 1952 | -- |
| NO. HOUSEHOLDS (HH) | | | | 5,904 | -- | 6,187 | -- |
| | AVERAGE HH SIZE, PERSONS | 2.4 | -- | 2.2 | -- | 2.2 | -- |
| | MEDIAN HH INCOME | $23,138 | -- | $29,272 | -- | $29,801 | -- |

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**San Francisco State University**

**Informed consent to participate in the following research study:**

**Relationship of airborne manganese exposure to neurobehavioral and health status of adults**

## A. PURPOSE AND BACKGROUND

The researcher of this study, Rosemarie Bowler, Ph.D., is a professor emerita of Psychology at San Francisco State University. The purpose of this study is to determine if there are negative health effects from exposure to airborne manganese and other chemicals in adults. You are being invited to participate in this study because you are a long term resident (10 or more years) of East Liverpool, Ohio and between the ages of 30 and 75. Your participation in this study is completely voluntary.

## B. PROCEDURES

If you agree to participate, the following will occur:

- All procedures will take place in our field office in East Liverpool.
- You will be interviewed about your health history. The interview will last approximately 15 minutes.
- You will be asked to complete questionnaires on your medical, social, and psychological history. This will take you about 60 minutes.
- You will be given tests used to measure multiple areas of cognitive functioning, such as general intellectual ability, memory, attention, learning, language, and visual and spatial skills. These tests will take no more than 75 minutes.
- Your motor functioning will be examined with tests of hand strength, balance and tremor, and dexterity. These will take approximately 15 minutes to complete.
- 12 mL (about 2 teaspoons) of blood will be drawn from a vein in your arm by a certified phlebotomist (a person trained to collect blood samples). Your blood will be securely shipped to, stored, and analyzed at the Centers for Disease Control and Prevention (CDC) Environmental Health Laboratory under the direction of the assistant chief of the laboratory, Kathleen Caldwell, Ph.D. Your blood will be analyzed for the following compounds: manganese, lead, mercury, and cadmium, in addition to iron and 2 liver enzymes.
- We will ask you to provide small amounts of your hair (a small sample taken from the back of the head underneath other hair so it will not be noticeable) as well as toenail clippings from all 10 toes. These samples will be analyzed in order to evaluate your exposure to metals.
- Your toenail and hair clippings will be securely shipped to, stored, and analyzed at the Harvard School of Public Health Trace Metals Laboratory. Your toenail clippings will be analyzed for levels of metals.
- Your participation in this study will take an average of 2.5 to 4.0 hours.

## C. RISKS

**1)** When blood is drawn, there is a risk of experiencing slight pain or a prick where the needle punctures the skin. There is also a slight risk of bruising or an infection where the needle punctures the skin. In rare cases, some people may experience lightheadedness, nausea, or fainting. The certified phlebotomist is trained in recognizing and dealing with such reactions. A licensed medical doctor (M.D.) will be on call nearby at all times and will give a consultation in case of a medical emergency for appropriate emergency medical care.

**2)** Participation in research may involve some possibility of loss of privacy. This risk will be reduced to the extent possible. More information about this risk and how we will reduce it appears in the confidentiality section below.

**3)** You may feel slight fatigue during testing. Should this occur, you can choose to take a break or discontinue testing at any point.

**4)** Some of the questions in the questionnaires may be personal and sensitive in nature. You are not required to answer a particular question if you feel uncomfortable.

**5)** It is possible that results from the blood analysis could reveal serious health problems that you are not aware of. After the analysis, you will be given a report indicating all your test results, and if anything serious is found, you are advised to consult with your family doctor or a local healthcare provider.

**6)** There may be risks and discomforts that are not yet known.

**7)** The researchers, research team and sponsors of this project will not provide medical care to participants nor will they cover the cost of medical care for participants.

## D. WHAT WILL HAPPEN IF YOU ARE INJURED BY THIS RESEARCH?

Theoretically, any research could involve a chance of personal injury. If such problems occur, the EPA cannot assist with the costs of the medical care.

Neither SFSU, nor the U.S. EPA has set aside funds to pay you for any such injuries, or for the related medical care. If you believe you have suffered a research-related injury, you have the right to pursue legal remedy if you believe that your injury justifies such action. The Federal Tort Claims Act, 28 U.S.C. S 2671 et seq., provides for money damages against the United States when property loss or personal injury results from the negligent or wrongful act or omission of any employee of the EPA while acting within the scope of his or her employment.

Signing this consent form does not waive any of your legal rights or release the investigator, the sponsor, the institution, or its agents from liability for negligence. If a research-related injury occurs, you should contact Howard Kehrl, the Director of the EPA NHEERL Human Research Protocol Office at 919-966-6208 or the Office for the Protection of Human Subjects at San Francisco State University, at 415-338-1093 or protocol@sfsu.edu.

## E. CONFIDENTIALITY

Your information will be handled confidentially. Your name will not be used in any published reports about this study. Your results will be entered into a computer database without your name or other identifiers. An ID number will be assigned to all of your test results and only Professor Rosemarie Bowler will be aware of your identity and ID number. The data will be handled only by research staff, all of whom will sign a special confidentiality contract, and will be entered in a password-protected computer database. All research records and test results will be stored in locked file cabinets. All electronic data and results will be kept in an encrypted document on a password-protected computer. Your information will not be released unless subpoenaed by a court of law. All data will be maintained for approximately 5 years in hard copy with access limited to only authorized individuals. The electronic data will be securely stored indefinitely. Unauthorized access will be reported to the relevant parties (participants, stakeholders). Electronic data will be saved on a device that has the appropriate security safeguards (password protection, etc).

## F. DIRECT BENEFITS

You will receive the test results in writing, which you can send to your physician. We will indicate whether any results are of concern. If abnormalities are found, you will be referred to your family physician.

## G. COSTS

There is no cost to you for participating in this research, aside from the transportation costs of coming to the appointment. Transportation costs involved in come to the field office will not be reimbursed. Medical care will not be provided by the researchers or research team nor will medical care costs be covered.

## H. COMPENSATION

You will be presented with a $50 gift card, as a token of appreciation for your participation in the study. Early withdrawal from the study or incompletion of major parts of the study will not be compensated monetarily.

## I. ALTERNATIVES

The alternative is not to participate in the research.

## J. QUESTIONS

You have spoken with Professor Rosemarie Bowler or one of her collaborators about this study and have had your questions answered. If you have any further questions about the study, you may contact the researcher by email at rbowl@sfsu.edu or by phone at 510-236-5599. Questions about your rights as a study participant, or comments or complaints about the study also may be addressed to the Office for the Protection of Human Subjects at San Francisco State University, at 415-338-1093 or protocol@sfsu.edu.

## K. CONSENT

**You have been given a copy of this consent form to keep.**

**PARTICIPATION IN THIS RESEARCH STUDY IS VOLUNTARY. You are free to decline to participate in this research study. You may withdraw from this study at any point without penalty. Even if you sign, you may stop at any time. Your decision to take part in this research will have no influence on your present or future status at San Francisco State University.**

Name _____

Signature _____ Date _____
Participant

Signature _____ Date _____
Researcher

Rosemarie Bowler, Ph.D.
8371 Kent Drive.
El Cerrito, CA 94530
Tel: 510/236-5599
Fax: 510/236-3370

August 9, 2011

RE: **East Liverpool Community Health Study**

**XXXX or current resident**
**Street Address**
**City, State Zip**

Dear XXXX or current resident,

My name is Professor Rosemarie Bowler, a faculty member at San Francisco State University in the Psychology Department. You may have seen in the local media that we are conducting research on the potential health effects of exposure to manganese in adults in your community. To examine these health effects, we are recruiting 100 adults in East Liverpool for participation. You have been randomly selected as a possible participant in our study. Any two members of your household between 30-75 years of age are invited to take part in study.

Each person participating in the study will receive a $50.00 gift card as a token of our appreciation. Additionally, we will give you your personal results of the health screening. The total time commitment we ask of you may be between 2½ to 4 hours. Testing is taking place at the Motor Lodge on 2340 Dresden Ave. in East Liverpool on November 4th, 5th, 6th & 7th mornings and afternoons. Participation in this study will involve asking you about your health and residential history, sleep, diet, and mood status. We also ask you to allow us to give you some tests to measure cognitive functioning, including memory, attention, learning, and visual/spatial skills. We will also be giving some tests of dexterity and strength. An expert movement neurologist will assess you briefly and a physician will review your medical history. Additionally, we will ask you for permission to draw a small blood sample, which will be analyzed in a certified laboratory for levels of manganese and other chemicals and that you provide a small sample of your hair and toenail clippings from each toe, which will be analyzed in a certified laboratory for levels of metals. All of your information will be kept confidential.

This research is being conducted with support from many partners, including the Ohio Department of Health, the mayor of East Liverpool, the East Liverpool City Health District's health commissioner, Jelayne Dray, the Region 5 Environmental Protection Agency (EPA), and Dr. Michelle Colledge of the Agency for Toxic Substances and Disease Registry.

If you are interested in participating in the study, please complete the enclosed self-addressed stamped postcard with your name, phone number, and email if you use it, and mail it to us at your earliest convenience. Alternatively, you can send us an email with your name, address, and phone number at ohstudy@sfsu.edu. Once we receive this card from you we will contact you by phone and a representative of our study team will ask you a few questions to determine if your background meets the study participation criteria, e.g., not having a severe, advanced major illness. We will also answer any questions you might have about the study.
Thank you for considering participating in the East Liverpool Community Health Study!

Sincerely,

Rosemarie L. Bowler, Ph.D.

Rosemarie Bowler, Ph.D.

# East Liverpool Phone Recruitment Script

Hello, my name is _____. I am a _____ at San Francisco State University in the Psychology Department. We are conducting research on the potential health effects of exposure to manganese in adults. This study is supported by the United States Environmental Protection Agency, or USEPA, the Ohio Department of Health, the Ohio EPA, as well as the Columbiana County Health Department. You may have attended or heard about the town meeting where we discussed the study. I am calling because you live in proximity to some of the warehouses that may release manganese and other chemicals into the air and there is concern that this may have a negative health effect. Therefore, we would like you to consider allowing us to test your health. We are recruiting 100 adults in your town to participate in our study.

For this study we are only recruiting current residents of East Liverpool. Are you currently living in East Liverpool? **[IF YES]** And have you lived there for at least 10 years?

**[IF NO]** Unfortunately, we are only looking for residents who have been living in the community for at least 10 years, so we cannot ask you to participate. Thank you very much for you time, and have a great morning/afternoon/evening.

**[IF YES]** Great. Now I would like to describe to you some of the details of the study and also ask some questions to determine if you are eligible to participate in the study. Regardless of whether you are chosen for the study or not, this information will be kept strictly confidential. Only authorized researchers will have access to it, and it will be stored in a secure locked cabinet in the investigator's office. Even if you are ineligible to participate, your information will be kept in a locked file cabinet in the investigator's office and will be destroyed after 5 years. Would you like to continue?

Participation in this study will involve a brief interview about your health history, in addition to questionnaires regarding your medical, social, and psychological history. You would also be given tests to measure areas of cognitive functioning, including memory, attention, learning, and visual/spatial skills. We will also ask you to complete a brief neurological test of movement. Additionally, we will ask you for permission to collect a small sample of your hair, to collect your toenail clippings and draw a small amount of blood. The hair, toenails, and blood samples will be analyzed in a certified laboratory for manganese and other chemicals. The total time commitment would be approximately 2.5-4 hours.

If you're willing to participate and you are selected to be in our study, upon completion we will present you with a $50 gift card as a token of our appreciation for your time. At a later time we will also notify you of your test results.

Would you be willing to answer some screening questions to determine your eligibility for our research study?

**[IF NO]** Thank you very much for your time and have a great morning/afternoon/evening.

**[IF YES]** Now I would like to ask the questions that I mentioned before. It should only take a few moments.

Sex: M F Age: _____ Years of Education: _____

Ethnicity: _____

1. Have you ever lived outside of East Liverpool, Ohio? Yes/No
2. Have you ever worked for S.H. Bell? Yes/No
3. Have you ever lived in Marietta? Yes/No
4. Have you ever worked in Eramet Marietta Inc? Yes/No
5. Have you ever had any major exposure, which required a hospital visit, to
   Pesticides? Yes/No If yes, Name if you know?_____
   Fungicides? Yes/No If yes, Name if you know?_____
   Herbicides? Yes/No If yes, Name if you know?_____
   Carbon monoxide? Yes/No
   Heavy metals? Yes/No Name if you know?_____
6. Have you ever had a head injury or stroke? Yes/No
7. If so, did you require a hospital visit for more than 1 day? Yes/No
8. Have you ever been told by a doctor that you have:
   Parkinson's disease? Yes/No
   Huntington's disease? Yes/No
   Epilepsy? Yes/No
   Brain surgery? Yes/No
   Encephalitis? Yes/No
   Meningitis? Yes/No
   Multiple sclerosis? Yes/No
   Chronic liver disease? Yes/No
9. Have you ever undergone electroconvulsive treatment? Yes/No
10. Have you ever been told by a doctor that you have:
    Bipolar disorder? Yes/No
    Alzheimer's disease? Yes/No
    Schizophrenia or psychoses? Yes/No
11. Are you currently being treated for alcohol or drug dependence? Yes/No
12. For women under 49 years of age: Are you currently pregnant or breastfeeding? Yes/No

If you are selected to be in the study, we will be contacting you again by phone 6-8 weeks prior to the study in order to set up an appointment. If you would like to contact us in the meantime, we can be reached at 510-236-5599 or at this email address:

ohstudy@sfsu.edu. Thank you again for your interest, and have a great morning/afternoon/evening

## Telephone Appointment Reminder Script—East Liverpool

Hello Mr./Ms. XXXX,
My name is _____. I am calling to remind you about your appointment to participate in our research study on the potential health effects of exposure to manganese in adults. Your appointment is at XX am/pm on Day/Month/Year. The appointment will last an average of 2.5 to 4.0 hours. We hope to see you at that time. The address of the location is XXXXXXXX.

Please make sure to bring your glasses, if you wear any, and a list of all medications you are currently taking.

If you have any questions, need directions, or need to cancel the appointment, you can contact us at (510) 236-5599

Thank you for your time.

Rosemarie Bowler, Ph.D.
8371 Kent Drive
El Cerrito, CA 94530
Tel: 510/236-5599
Fax: 510/236-3370

SAMPLE East Liverpool Feedback Letter

Dear XXXXX,

Thank you again for participating in the East Liverpool Community Health Study investigating the possible health effects of manganese exposure in adults. Enclosed you will find your personal results of the neurological and neuropsychological testing, as well as the results of your blood analysis. Thank you for providing your information to us. If you have questions about your individual results, please email your questions to:ohstudy@sfsu.edu or you can contact me at 510-236-5599.

We very much appreciate your participation in this community study of airborne manganese exposure in adults. It has been a privilege to have your cooperation in our study and we encourage you to contact us if you have additional questions or concerns you would like to discuss.

Sincerely,

Rosemarie Bowler, Ph.D., M.P.H.

**Dear «First_Name_1» «Last_Name_1»**
The tables below show the behavioral and laboratory test results from your participation in the 2011 East Liverpool Community Health study investigation of effects of air manganese exposure on adults in the community of East Liverpool, Ohio.

## Neuropsychological & Neurological Test Results:

| Area of function: | Description: | Results: |
|---|---|---|
| Motor Speed | Speed of performance of both hands | Wnl (within normal range) |
| Other Motor | Strength, manual dexterity, and tremor | Outside of normal range |
| Movement | Body stability, muscle tone, reflexes | Wnl (within normal range) |
| Attention | Attention, concentration, short-term memory | Wnl (within normal range) |
| Visual Memory | Long-term visual memory | Wnl (within normal range) |
| Auditory Memory | Long-term auditory memory | Outside of normal range |
| Cognitive Flexibility | Ability to perform complicated tasks | Wnl (within normal range) |
| Mood | Emotional functioning | Wnl (within normal range) |

If any of your test results are different from those found in the general population (outside of the normal range), you are advised to consult with your family doctor or a local healthcare provider. Please note that any medical care will be at your own expense. Note: Test results outside of the normal range may not result in a diagnosis.

Rosemarie Bowler, Ph.D.
8371 Kent Drive
El Cerrito, CA 94530
Tel: 510/236-5599
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## Blood Analyses Results:

| Lab test | Your Value | Found in General Population |
|---|---|---|
| Manganese (Mn) [1] | X µg/L | 4.0 to 15 µg/L |
| Lead (Pb) [2] | X µg/dL | 1.40 to 4.20 µg/dL |
| Cadmium (Cd) [2] | X µg/L | 0.3 to 1.3 µg/L |
| Mercury (Hg) [2] | X µg/L | 0.3 to 1.9 µg/L |
| Ferritin (Ferr-S) [3] | X ng/mL | Female: 10 – 120 ng/mL<br>Male: 20 – 250 ng/mL |

[1] http://www.atsdr.cdc.gov/toxprofiles/tp151.html – Chapter 1, p 8
[2] Based on National Health and Nutrition Survey years 2003-2004, U.S. general population upper 50th and 95th percentile.
Note: The measurement of an environmental chemical in a person's blood does not by itself mean that the chemical causes disease

## Toenail Analyses Results:

| Lab test | Your Value | Found in General Population |
|---|---|---|
| Manganese (Mn) | XXX | Normal values are not yet fully established |

## Hair Analyses Results:

| Lab test | Your Value | Found in General Population |
|---|---|---|
| Manganese (Mn) | XXX | Normal values are not yet fully established |

ID_____

# Environmental Worry Scale

| Please √ only one | Not at all true | Barely true | Moderately true | Exactly true |
|---|---|---|---|---|
| **1.** I don´t worry about being hurt by chemicals | ❑ | ❑ | ❑ | ❑ |
| **2.** I feel worried about toxic effects on my body which might result in losing some of my intellectual abilities. | ❑ | ❑ | ❑ | ❑ |
| **3.** Many people tend to overreact to the threat of environmental toxins. | ❑ | ❑ | ❑ | ❑ |
| **4.** Poor memory can be a direct result of too much exposure to chemicals | ❑ | ❑ | ❑ | ❑ |
| **5.** Being exposed to most chemicals for a long time does not cause serious diseases. | ❑ | ❑ | ❑ | ❑ |

36139

Name: _____

(For office use.)

## Satisfaction with Life Scale

Below are five statements that you may agree or disagree with. Using the 1-7 scale to the right, indicate your agreement by filling in the appropriate bubble next to each item. Please be open and honest in your responding.

**Scale:**
**1 = Strongly disagree**
**2 = Disagree**
**3 = Slightly disagree**
**4 = Neither agree nor disagree**
**5 = Slightly agree**
**6 = Agree**
**7 = Strongly agree**

| | Strongly disagree | Disagree | Slightly disagree | Neither agree nor disagree | Slightly agree | Agree | Strongly agree | |
|---|---|---|---|---|---|---|---|---|
| 1 | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | In most ways my life is close to my ideal. |
| 2 | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | The conditions of my life are excellent. |
| 3 | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | I am satisfied with my life. |
| 4 | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | So far I have gotten the important things I want in life. |
| 5 | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | If I could live my life over, I would change almost nothing. |

## Quality of Life Scale

**1** Would you say that in general your health is: (Fill in appropriate bubble.)

◯ **Excellent** ◯ **Very good** ◯ **Good** ◯ **Fair** ◯ **Poor**

**For items 2-4 below, please write in one number in each box, e.g., 3 days =** **0 3**

**2** Regarding your physical health, which includes physical illness and injury, for how many days during the past 30 days was your physical health not good? ☐☐ **0-30 days**

**3** Regarding your mental health, which includes stress, depression, and problems with emotions, for how many days during the past 30 days was your mental health not good? ☐☐ **0-30 days**

**4** During the past 30 days, for about how many days did poor physical or mental health keep you from doing your usual activities, such as self-care, work, or recreation? ☐☐ **0-30 days**

ID:_____

# Health Study Questionnaire

Please complete the attached questionnaire.

Your answers will be kept confidential.

Ask a staff person if you are not sure about any of the questions.

You can skip any questions you prefer not to answer.

You may be interrupted if a tester needs you for another test, but can continue to answer the questionnaire items after this interruption.

**Thank you for completing the questionnaire.**

ID:_____

# Health Study Questionnaire

## SECTION I: RESIDENCE INFORMATION

**1.** How many years have you lived in East Liverpool? _____ **years**

**2.** Address: **(Please list the addresses of the last 3 places you have lived for more than a year)**

**A. Current Address:**
Street address _____ From: month _____ year _____
City _____ State ___ ZIP _____ To: Present

**B. Previous (most recent) address:**
Street address _____ From: month _____ year _____
City _____ State ___ ZIP _____ To: month _____ year _____

**C. Previous address:**
Street address _____ From: month _____ year _____
City _____ State ___ ZIP _____ To: month _____ year _____

**D. If you have lived at more than 3 addresses for more than 1 year, please let us know and we will provide you with a supplemental residency sheet.**

**3.** Are you on the public water supply?
- ❑ Yes
- ❑ No

## SECTION II: SYMPTOMS

**Are you experiencing any of the following symptoms?**
(**Please** √ and, IF YES, write in **year** started.)

ID:_____

| | NO | YES | When did you experience it for the first time? (year) | How many times did you experience this in the LAST MONTH? |
|---|---|---|---|---|
| 1. Problems sleeping | ❑ | ❑ | | |
| 2. Problems falling asleep | ❑ | ❑ | | |
| 3. Waking up too often | ❑ | ❑ | | |
| 4. Waking up too early | ❑ | ❑ | | |
| 5. Having nightmares | ❑ | ❑ | | |
| 6. Night sweats | ❑ | ❑ | | |
| 7. Difficulty waking up in the morning | ❑ | ❑ | | |
| 8. Difficulty staying awake during the day | ❑ | ❑ | | |
| 9. Awakening with muscle cramps | ❑ | ❑ | | |
| 10. Blurred vision | ❑ | ❑ | | |
| 11. Changes in handwriting | ❑ | ❑ | | |
| 12. Changes in sense of smell | ❑ | ❑ | | |
| 13. Changes in sense of taste | ❑ | ❑ | | |
| 14. Changes in walking | ❑ | ❑ | | |
| 15. Confusion or feeling lost | ❑ | ❑ | | |
| 16. Cough | ❑ | ❑ | | |
| 17. Cramping in legs | ❑ | ❑ | | |
| 18. Dark vision | ❑ | ❑ | | |
| 19. Diarrhea | ❑ | ❑ | | |
| 20. Dim vision | ❑ | ❑ | | |
| 21. Difficulty chewing | ❑ | ❑ | | |
| 22. Difficulty concentrating | ❑ | ❑ | | |
| 23. Difficulty driving because of feeling dizzy | ❑ | ❑ | | |
| 24. Difficulty getting out of chairs | ❑ | ❑ | | |
| 25. Difficulty sitting up straight | ❑ | ❑ | | |
| 26. Difficulty turning in bed | ❑ | ❑ | | |
| 27. Difficulty with skilled movements | ❑ | ❑ | | |
| 28. Difficulty writing | ❑ | ❑ | | |
| 29. Excessive perspiration | ❑ | ❑ | | |

**Are you experiencing any of the following symptoms?**
(**Please** √ and, IF YES, write in **year** started.)

| | NO | YES | When did you experience it for the first time? (year) | How many times did you experience this in the LAST MONTH? |
|---|---|---|---|---|
| 30. Excessive salivation | ❑ | ❑ | | |
| 31. Facial expression changes | ❑ | ❑ | | |
| 32. Facial muscle tightness | ❑ | ❑ | | |
| 33. Feeling anxious | ❑ | ❑ | | |
| 34. Feeling depressed | ❑ | ❑ | | |
| 35. Feeling irritable | ❑ | ❑ | | |
| 36. Feeling lightheaded or dizzy | ❑ | ❑ | | |
| 37. Fever, chills | ❑ | ❑ | | |
| 38. Hand or foot tapping | ❑ | ❑ | | |
| 39. Headaches at least twice a week | ❑ | ❑ | | |
| 40. Joint pain or swelling | ❑ | ❑ | | |
| 41. Loss of consciousness (fainting) | ❑ | ❑ | | |
| 42. Loss of coordination or balance | ❑ | ❑ | | |
| 43. Loss of muscle strength in arms/hand | ❑ | ❑ | | |
| 44. Loss of muscle strength in legs/feet | ❑ | ❑ | | |
| 45. Loss of sense of smell | ❑ | ❑ | | |
| 46. Lower tolerance for alcohol | ❑ | ❑ | | |
| 47. Metallic taste in mouth | ❑ | ❑ | | |
| 48. Migraine headaches | ❑ | ❑ | | |
| 49. Monotonous voice | ❑ | ❑ | | |
| 50. Muscle aches | ❑ | ❑ | | |
| 51. Muscle twitching | ❑ | ❑ | | |
| 52. Muscular rigidity | ❑ | ❑ | | |
| 53. Nausea not cause by something you ate | ❑ | ❑ | | |
| 54. Noticeable change in personality | ❑ | ❑ | | |
| 55. Numbness/tingling in fingers or feet, for more than one day | ❑ | ❑ | | |
| 56. Sexual dysfunction | ❑ | ❑ | | |
| 57. Shortness of breath on exertion | ❑ | ❑ | | |
| 58. Skin rash | ❑ | ❑ | | |

**Are you experiencing any of the following symptoms?**
(**Please** √ and, IF YES, write in **year** started.)

| | NO | YES | When did you experience it for the first time? (year) | How many times did you experience this in the LAST MONTH? |
|---|---|---|---|---|
| 59. Slowness of movement | ❑ | ❑ | | |
| 60. Slurred speech | ❑ | ❑ | | |
| 61. Stomach cramps / stomach pain | ❑ | ❑ | | |
| 62. Tremors or Shakiness (temporary) | ❑ | ❑ | | |
| 63. Tremors or Shakiness (long term) | ❑ | ❑ | | |
| 64. Trouble remembering things | ❑ | ❑ | | |
| 65. Urinary or Bowel incontinence | ❑ | ❑ | | |
| 66. Vomiting | ❑ | ❑ | | |
| 67. Wheezing or whistling in chest | ❑ | ❑ | | |
| 68. Weight fluctuation | ❑ | ❑ | | |
| 69. Respiratory problems on **'bad air'** days | ❑ | ❑ | | |
| 70. Bringing phlegm from chest into throat | ❑ | ❑ | | |
| 71. Dizziness when in the presence of **gas** | ❑ | ❑ | | |
| 72. Headaches when in the presence of **gas** | ❑ | ❑ | | |
| 73. Dizziness when in the presence of **paint** | ❑ | ❑ | | |
| 74. Headaches when in the presence of **paint** | ❑ | ❑ | | |

**75.** When you are driving and have just passed a light, do you worry that it was red? (please √ one)

❑ Never **(skip to 76 below)** ❑ Occasionally
❑ Rarely ❑ Frequently

**A.** When did you experience it for the first time? **(year)** _____

**B. How** many times did you experience this in the LAST MONTH? _____ **times**

**76.** Do you consider yourself allergic or unusually sensitive to everyday chemicals like those in household cleaning supplies, paints, perfumes, soaps, garden sprays or things like that?

❑ Yes
❑ No **(IF NO, skip to MEDICAL HISTORY section)**
❑ Not Sure/Don't' Know **(IF NOT SURE, skip to MEDICAL HISTORY section)**

**77. If YES,** how old were you when you first noticed this sensitivity? **_____ (age)**

**IF** you don't remember, did you have it:

- ❑ Entire life
- ❑ Don't remember what age, but not entire life
- ❑ Don't know/ Not sure

**78.** Was there something that happened when you were that age that first triggered this sensitivity?

- ❑ Yes
- ❑ No **(IF NO, skip to MEDICAL HISTORY section)**
- ❑ Not Sure/Don't' Know **(IF NOT SURE, skip to MEDICAL HISTORY section)**

**79. IF YES, what was it?** _____

## SECTION III: MEDICAL HISTORY

**Have you ever been diagnosed <u>by a doctor</u> as having any of the following illnesses or conditions?**
(**Please** √ and, **IF YES**, write in the **year** when diagnosed.)

| | NO | YES | Year diagnosed | Had it within the last year? No | Had it within the last year? YES | |
|---|---|---|---|---|---|---|
| 1. Acute Bronchitis | ❑ | ❑ | _____ | ❑ | ❑ | **How many times in last year?** _____ |
| 2. Pleurisy | ❑ | ❑ | _____ | ❑ | ❑ | |
| 3. Tuberculosis | ❑ | ❑ | _____ | ❑ | ❑ | |
| 4. Chest Injury | ❑ | ❑ | | ❑ | ❑ | |
| 5. Pneumonia | ❑ | ❑ | _____ | ❑ | ❑ | **How many times in last year?** _____ |
| 6. Chronic Bronchitis | ❑ | ❑ | | ❑ | ❑ | **How many times in last year?** _____ |
| 7. Emphysema | ❑ | ❑ | _____ | ❑ | ❑ | |
| 8. Asthma | ❑ | ❑ | _____ | ❑ | ❑ | **How many times in last year?** _____ |
| 9. Hay fever | ❑ | ❑ | _____ | ❑ | ❑ | |

**Have you ever been diagnosed <u>by a doctor</u> as having any of the following illnesses or conditions?**
(**Please** √ and, **IF YES**, write in the **year** when diagnosed.)

| | NO | YES | Year diagnosed | Had it within the last year? No | Had it within the last year? YES | |
|---|---|---|---|---|---|---|
| 10. High blood pressure | ❑ | ❑ | _____ | ❑ | ❑ | |
| 11. Heart trouble | ❑ | ❑ | _____ | ❑ | ❑ | |
| 12. Heart attack | ❑ | ❑ | _____ | ❑ | ❑ | **How many times in last year?** _____ |
| 13. Chest pain with exertion | ❑ | ❑ | _____ | ❑ | ❑ | |
| 14. Heart valve disease | ❑ | ❑ | _____ | ❑ | ❑ | |
| 15. Bone or joint cancer | ❑ | ❑ | _____ | ❑ | ❑ | |
| 16. Brain cancer | ❑ | ❑ | _____ | ❑ | ❑ | |
| 17. Breast cancer | ❑ | ❑ | _____ | ❑ | ❑ | |
| 18. Cancer of esophagus (swallowing tube), stomach, intestines, colon, rectum, liver, pancreas, or other digestive organs | ❑ | ❑ | _____ | ❑ | ❑ | |
| **IF YES,** which type?_____ | | | | | | |
| 19. Kidney or bladder cancer | ❑ | ❑ | _____ | ❑ | ❑ | |
| 20. Leukemia | ❑ | ❑ | _____ | ❑ | ❑ | |
| 21. Lymphoma or lymph system cancer | ❑ | ❑ | _____ | ❑ | ❑ | |
| 22. Lung or chest cancer | ❑ | ❑ | _____ | ❑ | ❑ | |
| 23. Multiple myeloma | ❑ | ❑ | _____ | ❑ | ❑ | |
| 24. Male or female organ cancer | ❑ | ❑ | _____ | ❑ | ❑ | |
| **IF YES,** which type?_____ | | | | | | |
| 25. Mouth or throat cancer | ❑ | ❑ | _____ | ❑ | ❑ | |

**Have you ever been diagnosed <u>by a doctor</u> as having any of the following illnesses or conditions?**
(**Please** √ and, **IF YES**, write in the **year** when diagnosed.)

| | NO | YES | Year diagnosed | Had it within the last year? No | YES | |
|---|---|---|---|---|---|---|
| 26. Nasal cancer | ❑ | ❑ | _____ | ❑ | ❑ | |
| 27. Skin cancer | ❑ | ❑ | _____ | ❑ | ❑ | |
| 28. Thyroid cancer | ❑ | ❑ | _____ | ❑ | ❑ | |
| 29. Cataracts | ❑ | ❑ | _____ | ❑ | ❑ | |
| 30. Glaucoma | ❑ | ❑ | _____ | ❑ | ❑ | |
| 31. Other eye problems (not related to glasses or contacts) | ❑ | ❑ | _____ | ❑ | ❑ | |
| **IF YES,** which type?_____ | | | | | | |
| 32. Anemia | ❑ | ❑ | _____ | ❑ | ❑ | **How many times in last year?** _____ |
| 33. Psychiatric / nervous disorder | ❑ | ❑ | _____ | ❑ | ❑ | |
| **IF YES,** which type?_____ | | | | | | |
| Were you given medication? | ❑ | ❑ | _____ | | | |
| **IF YES,** which medication?_____ | | | | | | |
| 34. Seizure disorder | ❑ | ❑ | _____ | ❑ | ❑ | |
| 35. Diabetes | ❑ | ❑ | _____ | ❑ | ❑ | |
| 36. Hepatitis, jaundice or other liver disease | ❑ | ❑ | _____ | ❑ | ❑ | |
| 37. Allergies | ❑ | ❑ | _____ | ❑ | ❑ | |
| **IF YES,** which type?_____ | | | | | | |
| 38. Skin rashes | ❑ | ❑ | _____ | ❑ | ❑ | **How many times in last year?** _____ |
| 39. Diseases of bones, joints, muscles | ❑ | ❑ | _____ | ❑ | ❑ | |

ID:_____

**Have you ever been diagnosed <u>by a doctor</u> as having any of the following illnesses or conditions?**
(**Please** √ and, **IF YES**, write in the **year** when diagnosed.)

| | NO | YES | Year diagnosed | Had it within the last year? No | YES | |
|---|---|---|---|---|---|---|
| 40. Kidney problems / infection | ❑ | ❑ | | ❑ | ❑ | |
| 41. Bladder infection | ❑ | ❑ | | ❑ | ❑ | **How many times in last year?** _____ |
| 42. Cold sores or mouth ulcers | ❑ | ❑ | | ❑ | ❑ | **How many times in last year?** _____ |
| 43. Blood in urine | ❑ | ❑ | | ❑ | ❑ | |
| 44. Thyroid disease | ❑ | ❑ | | ❑ | ❑ | |
| 45. Head injury | ❑ | ❑ | | ❑ | ❑ | |
| 46. Asbestosis | ❑ | ❑ | | ❑ | ❑ | |
| 47. Rheumatic fever | ❑ | ❑ | | ❑ | ❑ | |
| 48. Fainting spells | ❑ | ❑ | | ❑ | ❑ | **How many times in last year?** _____ |
| 49. Sinus trouble / Sinusitis | ❑ | ❑ | | ❑ | ❑ | **How many times in last year?** _____ |
| 50. Back or spine problems | ❑ | ❑ | | ❑ | ❑ | |
| 51. Swollen lymph nodes | ❑ | ❑ | | ❑ | ❑ | **How many times in last year?** _____ |
| 52. Aplastic anemia | ❑ | ❑ | | ❑ | ❑ | |
| 53. Niemann-Pick's disease | ❑ | ❑ | | ❑ | ❑ | |
| 54. Alzheimer's disease | ❑ | ❑ | | ❑ | ❑ | |
| 55. Amyotrophic Lateral Sclerosis (ALS), aka Lou Gehrig's disease | ❑ | ❑ | | ❑ | ❑ | |
| 56. Huntington's chorea | ❑ | ❑ | | ❑ | ❑ | |
| 57. Multiple Sclerosis | ❑ | ❑ | | ❑ | ❑ | |
| 58. Parkinson's disease | ❑ | ❑ | | ❑ | ❑ | |

**Have you ever been diagnosed <u>by a doctor</u> as having any of the following illnesses or conditions?**
(**Please** √ and, **IF YES**, write in the **year** when diagnosed.)

| | NO | YES | Year diagnosed | Had it within the last year? No | YES |
|---|---|---|---|---|---|
| 59. Autoimmune Connective Tissue Disorders (Lupus, Rheumatoid arthritis) | ❑ | ❑ | _____ | ❑ | ❑ |
| 60. Tremor disorder | ❑ | ❑ | _____ | ❑ | ❑ |
| 61. Silicosis, aka Grinder's disease or Potter's rot | ❑ | ❑ | _____ | ❑ | ❑ |
| 62. Other major illness | ❑ | ❑ | _____ | ❑ | ❑ |

**IF YES,** which type?_____

63. Have you been hospitalized in the last 5 years? **No** ❑ **Yes**❑ **IF YES** what year?_____

**IF YES**, what was the condition? _____

If you were hospitalized more than once in 5 years, please list these below:

## SECTION IV: MEDICATIONS

1. Have you taken any medication in the last 24 hours (including prescription and over-the-counter)?

❑ Yes
❑ No **(IF NO, skip to question 4)**

2. What medication(s) did you take in the last 24 hrs.?_____

3. When did you first take that medication? _____**/**_____ **(month/year)**

4. Have you taken the following **over-the-counter** medications? If YES, please write the name/brand.

ID:_____

| Over-the-counter | NO | YES | If YES, please write name/brand | √ if taken in last month | If YES, how many do/did you take? Per Year | Per Month | Per Day |
|---|---|---|---|---|---|---|---|
| **1.** Antacids or Stomach Medicine (Maalox, Mylanta, Tums, etc.) | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **2.** Cough Medicine | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **3.** Cold Medications | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **4.** Skin Medications or Creams | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **5.** Headache Medicines | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **6.** Sleeping Pills | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **7.** Pain Medications (Aspirin, Tylenol, Advil, etc.) | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **8.** Iron Supplements | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **9.** Vitamin Supplements with Iron | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **10.** Herbal Medicine | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **11.** Other: | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |

5. Have you taken the following **prescription** medications? If YES, please write the name/brand.

| Prescription | NO | YES | If YES, please write name/brand | √ if taken in last month | If YES, how many do/did you take? Per Year | Per Month | Per Day |
|---|---|---|---|---|---|---|---|
| **1.** Prescribed Antacids or Stomach Medicine | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **2.** Antibiotics | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **3.** Arthritis Medicine | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **4.** Blood Pressure Medicine | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **5.** Medications for Asthma | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |

| Prescription | NO | YES | If YES, please write name/brand | √ if taken in last month | If YES, how many do/did you take? Per Year | Per Month | Per Day |
|---|---|---|---|---|---|---|---|
| **6.** Heart Medicines (for heart problems or irregular heartbeat, etc.) | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **7.** Cholesterol Medicines (for lowering lipid, etc.) | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **8.** Diabetes Medicines | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **9.** Eye Medications | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **10.** Prescribed Headache Medicines | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **11.** Muscle Relaxants | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **12.** Medicine for Depression | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **13.** Medicine for Anxiety | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **14.** Prescribed Pain Medications | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **15.** Parkinson's/Tremor Medication (L-DOPA, Sinemet, Azilect, Mirapex, Mysoline, etc.) | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **16.** Other: | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |

## SECTION V: WORK HISTORY & BEHAVIORS

**1.** What is your current employment status? Please √ all that apply.

- ❑ Employed full-time
- ❑ Employed part-time
- ❑ Unemployed
- ❑ Homemaker
- ❑ Full-time student
- ❑ Part-time student
- ❑ Retired
- ❑ Disabled
- ❑ Other *(please specify)* _____

**2.** **<u>If you are disabled</u>,** please answer the following:

A. What date did you become disabled?___/_____ **(month/year)**

B. **How** did you become disabled?_____

_____

C. Please list any jobs and the time worked **since your disability**:

| **Position** | **Tasks** | **Duration** (example: 1975 to 1978) |
|---|---|---|
| | | |
| | | |

**3.** **If not currently employed,** are you receiving: *(please √ all that apply)*

- ❑ Not receiving any benefits/assistance
- ❑ Retirement
- ❑ Disability
- ❑ Other *(please specify)* _____
- ❑ AFDC
- ❑ General Assistance
- ❑ SSI

**4.** Please list your employers, starting with current or most recent employer, dates of employment, and position held:

**A.** _____ from____ to ____ Position_____

**B.** _____ from____ to ____ Position_____

**C.** _____ from____ to ____ Position_____

**D.** _____ from____ to ____ Position_____

**E.** _____ from____ to ____ Position_____

**5.** For how many months were you employed in the past 2 years? _____

**6.** Approximately how many days were you sick at home in the past 2 years? ____

**7.** Did any of your employment involve exposure to chemicals?

- ❑ Yes **(Please describe in the table below)**
- ❑ No **(Skip to question 8)**
- ❑ Not Sure/Don't' Know **(Skip to question 8)**

| Employer / Position | Duration (Please list years) | Type of chemical? | | | |
|---|---|---|---|---|---|
| | | Solvents | Pesticides | Metals | Not sure which type |
| _____ | _____ to _____ | ❑ | ❑ | ❑ | ❑ |
| _____ | _____ to _____ | ❑ | ❑ | ❑ | ❑ |
| _____ | _____ to _____ | ❑ | ❑ | ❑ | ❑ |
| _____ | _____ to _____ | ❑ | ❑ | ❑ | ❑ |

| **Have you ever participated in any of the following hobbies?** | **NO** | **YES** |
|---|---|---|
| **8.** Welding | ❑ | ❑ |
| **9.** Gardening | ❑ | ❑ |
| **10.** Painting | ❑ | ❑ |
| **11.** Ceramics/sculpting | ❑ | ❑ |
| **12.** Stained glass | ❑ | ❑ |
| **13.** Metal Work/Jewelry | ❑ | ❑ |
| **14.** Photo lab developing | ❑ | ❑ |

**15.** Have you had chemical exposure at home or while doing hobbies (not during work)?

❑ Yes **(IF YES, please describe below)**
❑ No **(IF NO, continue with question 16)**

**IF YES,** please describe and indicate when (year): _____

_____

_____

_____

**16. Do you currently smoke?**

- ❑ Yes **(IF YES, skip to question 19)**
- ❑ No

**17.** Have you ever smoked more than 100 cigarettes (or 5 packs) in your life?

- ❑ Yes
- ❑ No **(IF NO, skip to question 22)**

**18.** When did you stop smoking? _____/_____**(month/year)**

**19.** At what age did you begin smoking? _____

**20.** For how many years did you smoke? _____ **Years**

**21.** How many cigarettes per day (not packs)? _____ **cigarettes**

**22.** Does someone in your household smoke?

- ❑ Yes
- ❑ No

**23.** Do you drink alcoholic beverages?

- ❑ Yes
- ❑ No **(IF NO, skip to question 31)**

**24.** How long have you been consuming alcoholic beverages? ___ **years**

**25.** For each type of alcohol below, please indicate **on average** how many days a week you drink and how much you drink on those days that you do:

| **Type of alcohol:** | **Drink it? No** | **Yes** | **If YES, days per week** | **If Yes, drinks per day** |
|---|---|---|---|---|
| a. Beer (bottle) | ❑ | ❑ | _____ | _____ |
| b. Wine (glass) | ❑ | ❑ | _____ | _____ |
| c. Hard liquor (1½ oz.) | ❑ | ❑ | _____ | _____ |

**26.** Has there been a change in how your body reacts to alcohol?

- ❑ Yes
- ❑ No **(IF NO, skip to question 28)**

**27.** Can you tolerate:

- ❑ More
- ❑ Less

**28.** Has there has been any change in your drinking habits?

- ❑ Yes
- ❑ No **(IF NO, skip to question 31)**

**29.** In what year was the change in your drinking habits? _____

**30.** What was the change in your drinking habits? (please √ only one)

❑ Drink more now ❑ Drink less now ❑ No longer drink

**31.** Please estimate the number of hours spent per day in:

| | **Weekday** | | **Weekend** | |
|---|---|---|---|---|
| **SPRING / SUMMER** | **Average # of hours per day** | **# of hours of heavy physical exertion per day** | **Average # of hours per day** | **# of hours of heavy physical exertion per day** |
| a. Outdoors | _____ | _____ | _____ | _____ |
| b. Indoors | _____ | _____ | _____ | _____ |
| **FALL / WINTER** | **Average # of hours per day** | **# of hours of heavy physical exertion** | **Average # of hours per day** | **# of hours of heavy physical exertion** |
| a. Outdoors | _____ | _____ | _____ | _____ |
| b. Indoors | _____ | _____ | _____ | _____ |

**32.** In Spring / Summer, approximately how many **hours per day** do you **keep windows open?** _____ **hrs.**

**33.** In Spring / Summer, approximately how many **hours per day** do you **use an air conditioner?** _____ **hrs. (if no a/c, please enter 0)**

**34.** In Fall / Winter, approximately how many **hours per day** do you **keep windows open?** _____ **hrs.**

**35.** In Fall / Winter, approximately how many **hours per day** do you **use an air conditioner?** _____ **hrs. (if no a/c, please enter 0)**

**36.** On average, how many hours per night do you sleep? _____**hours**

**37.** In the past 12 months, have there been any major life events that have had an impact on your life (example: major illness, death of someone close)?

- ❑ Yes **(please describe in the box below)**
- ❑ No **(IF NO, skip to the DIET section below)**

**38.** Do you feel that this event(s) affected your physical health?

- ❑ Yes
- ❑ No

**39.** Do you feel that this event(s) affected your mental health?

- ❑ Yes
- ❑ No

# SECTION VI: DIET

As some foods contain naturally-occurring trace levels of manganese or iron, we are interested in knowing approximately how much you consume of these types of food in order to estimate your total body burden of manganese and iron. For each of these foods, please indicate approximately how much you consume each week on average. Please also indicate the approximate number of servings you have had in the last month, and in the last 3 months.

| **Meat and Poultry** | **Serving size** | **Approx. # of servings per week** | **Approx. # of servings in last month** | **Approx. # of servings in last 3 months** | **√ if you do not eat any** |
|---|---|---|---|---|---|
| 1. Beef, chuck, lean only, braised | 3 ounces | | | | ❑ |
| 2. Beef, tenderloin, roasted | 3 ounces | | | | ❑ |
| 3. Beef, eye of round, roasted | 3 ounces | | | | ❑ |
| 4. Pork, loin, broiled | 3 ounces | | | | ❑ |
| 5. Turkey, dark meat, roasted | 3½ ounces | | | | ❑ |
| 6. Turkey, light meat, roasted | 3½ ounces | | | | ❑ |
| 7. Chicken liver, cooked | 3½ ounces | | | | ❑ |
| 8. Chicken, leg, meat only, roasted | 3½ ounces | | | | ❑ |
| 9. Chicken, breast, roasted | 3 ounces | | | | ❑ |
| **Seafood** | **Serving size** | **Approx. # of servings per week** | **Approx. # of servings in last month** | **Approx. # of servings in last 3 months** | **√ if you do not eat any** |
| 10. Tuna, fresh bluefin, cooked, dry heat | 3 ounces | | | | ❑ |
| 11. Tuna, white, canned in water | 3 ounces | | | | ❑ |
| 12. Halibut, cooked, dry heat | 3 ounces | | | | ❑ |
| 13. Oysters, breaded and fried | 6 pieces | | | | ❑ |
| 14. Crab, blue crab, cooked, moist heat | 3 ounces | | | | ❑ |

| | | | | | |
|---|---|---|---|---|---|
| 15. Shrimp, mixed species, cooked, moist heat | 4 large | | | | ❑ |
| 16. Clams, breaded, fried | ¾ cup | | | | ❑ |
| **Vegetables** | **Serving size** | **Approx. # of servings per week** | **Approx. # of servings in last month** | **Approx. # of servings in last 3 months** | **√ if you do not eat any** |
| 17. Spinach, cooked | ½ cup | | | | ❑ |
| 18. Broccoli | ½ cup | | | | ❑ |
| 19. Swiss chard | ½ cup | | | | ❑ |
| 20. Bok Choy | ½ cup | | | | ❑ |
| 21. Beet greens, cooked | ½ cup | | | | ❑ |
| 22. Turnip greens | ½ cup | | | | ❑ |
| 23. Green Beans | ½ cup | | | | ❑ |
| 24. Peas | ½ cup | | | | ❑ |
| 25. Potato | ½ cup | | | | ❑ |
| 26. Sea Vegetables | ½ cup | | | | ❑ |
| **Fruits** | **Serving size** | **Approx. # of servings per week** | **Approx. # of servings in last month** | **Approx. # of servings in last 3 months** | **√ if you do not eat any** |
| 27. Watermelon | 1/8 melon | | | | ❑ |
| 28. Pineapple | 1 cup | | | | ❑ |
| 29. Dried Figs | 5 | | | | ❑ |
| 30. Dried Apricots | 5 | | | | ❑ |
| **Soy Products** | **Serving size** | **Approx. # of servings per week** | **Approx. # of servings in last month** | **Approx. # of servings in last 3 months** | **√ if you do not eat any** |
| 31. Soy Beans | ½ cup | | | | ❑ |
| 32. Tofu | ½ cup | | | | ❑ |
| 33. Tempeh | ½ cup | | | | ❑ |

| Grains | Serving size | Approx. # of servings per week | Approx. # of servings in last month | Approx. # of servings in last 3 months | √ if you do not eat any |
|---|---|---|---|---|---|
| 34. Wheat Pasta | 1 cup | | | | ❑ |
| 35. Brown Rice | 1 cup | | | | ❑ |
| 36. Bran Cereal | 1 cup | | | | ❑ |
| 37. Oatmeal | 1 cup | | | | ❑ |
| **Nuts, Seeds and Legumes** | **Serving size** | **Approx. # of servings per week** | **Approx. # of servings in last month** | **Approx. # of servings in last 3 months** | **√ if you do not eat any** |
| 38. Almonds | ¼ cup | | | | ❑ |
| 39. Peanuts | 3½ ounces | | | | ❑ |
| 40. Sunflower Seeds | 2 Tbsp | | | | ❑ |
| 41. Pumpkin Seeds | 2 Tbsp | | | | ❑ |
| 42. Pinto Beans | ½ cup | | | | ❑ |
| 43. Navy Beans | ½ cup | | | | ❑ |
| 44. Black eyed beans | ½ cup | | | | ❑ |
| 45. Lentils | ½ cup | | | | ❑ |
| 46. Chickpeas (Garbanzo Beans) | 7 ounces | | | | ❑ |
| **Beverages** | **Serving size** | **Approx. # of servings per week** | **Approx. # of servings in last month** | **Approx. # of servings in last 3 months** | **√ if you do not eat any** |
| 47. Tea | 1 cup | | | | ❑ |
| 48. Soy Milk | ½ cup | | | | ❑ |
| 49. Tomato Juice | ½ cup | | | | ❑ |
| 50. Prune Juice | ½ cup | | | | ❑ |

51. Do you grow your own fruits or vegetables in the soil at your residence?

❑ Yes

**IF YES, what percentage of the produce you eat is home-grown? _____%**

❑ No

# SECTION VII: ABOUT YOU

**1.** What is your sex?

- ❑ Male
- ❑ Female

**2.** What is your age? _____

**3.** What is your date of birth? _____**/**___**/**_____ **(month/day/year)**

**4.** What is your race/ethnicity?

- ❑ African-American
- ❑ Caucasian
- ❑ Hispanic/Chicano/Latino
- ❑ Asian or Pacific Islander
- ❑ Native American
- ❑ Other *(please specify)*_____

**5.** What is your current marital status?

- ❑ Single
- ❑ Married
- ❑ Divorced
- ❑ Widowed
- ❑ Living with significant other
- ❑ Other *(please specify)*_____

**6.** How many children do you have (including adopted and stepchildren)? _____

**7.** How many children live in your household? _____

**8.** Which of the following best describes the highest level of education you have attained?

- ❑ Less than 9th grade
- ❑ 9th-12th, no diploma
- ❑ High School Diploma/G.E.D.
- ❑ Some college, no degree
- ❑ Associate Degree
- ❑ 4-Yr./Bachelor's Degree
- ❑ Graduate Degree: (please circle)
  MA/MS Ph.D. MD JD

**9.** What was your **best** subject in school? _____

**10.** On average, what grades did you get in your **best** subject? _____

**11.** What was your **worst** subject in school?_____

**12.** On average, what grades did you get in your **worst** subject? _____

**13.** Have you ever been diagnosed with a learning disability?

- ❑ Yes **(IF YES, please specify)** _____
- ❑ No

**14.** Were you ever placed in a special education or remedial class?

- ❑ Yes
- ❑ No

**15.** Do you have health insurance?

- ❑ Yes
- ❑ No **(IF NO, skip to question 17)**

**16.** What type of insurance do you have?

- ❑ Private insurance
- ❑ Medicaid
- ❑ Medicare
- ❑ SSI
- ❑ Other (specify)_____

Name of insurance: _____

**17.** Please identify your primary doctor:

Doctor's name: _____

**18.** How many times have you seen a doctor or nurse in the last 12 months?_____ **Times**

**19.** What is your current **personal annual income** (from all sources)? *(please √one)*

- ❑ $0-9,999
- ❑ $10,000-19,999
- ❑ $20,000-29,999
- ❑ $30,000-39,999
- ❑ $40,000-49,999
- ❑ $50,000-59,999
- ❑ $60,000-69,999
- ❑ $70,000-79,999
- ❑ $80,000-89,999
- ❑ $90,000-99,999
- ❑ 100,000 or more

**20.** What is the annual **total income of your household**? *(please √ one)*

- ❑ $0-9,999
- ❑ $10,000-19,999
- ❑ $20,000-29,999
- ❑ $60,000-69,999
- ❑ $70,000-79,999
- ❑ $80,000-89,999

- ❑ $30,000-39,999
- ❑ $40,000-49,999
- ❑ $50,000-59,999
- ❑ $90,000-99,999
- ❑ 100,000 or more

**21.** How many persons were supported this past year by your total household income **indicated in question 19 above** (including yourself)? _____

If you would like us to know anything else about your experiences, please feel free to write a note in the space below.

**Thank you very much for your time!**

# San Francisco State University Protocol and Approval Package

SAN FRANCISCO STATE UNIVERSITY

OFFICE OF RESEARCH AND SPONSORED PROGRAMS
HUMAN AND ANIMAL PROTECTIONS

INSTITUTIONAL REVIEW BOARD

Administration 452
1600 Holloway Avenue
San Francisco, CA 94132

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Fax: 415/405-2474
E-mail: protocol@sfsu.edu
Web: http://research.sfsu.edu/protocol

Date: July 28, 2011

To: Rosemarie Bowler

Re: An Epidemiologic Health Study of Manganese Exposure in Adult Residents of East Liverpool, Ohio

The Institutional Review Board (IRB) at San Francisco State University has reviewed and approved the use of human subjects in the above protocol. You may proceed with your research as described in your protocol and as modified in any subsequent correspondence. Please honor your own discipline's professional code of conduct.

**Protocol Number:** H11-39

**Approval Date:** **July 28, 2011** **Non-Exempt Full Committee Review**
Original Contingent Approval Date from Committee: July 20, 2011
**Expiration Date:** This approval expires on **July 19, 2012**

If the project will continue, it must be renewed **before** the expiration date. Please allow at least six weeks for processing the renewal application. **Data cannot be used in the research if collected after the expiration date, before the protocol has been renewed.**

**Completion:** Upon completion of the project, a Study Completion Form must be submitted to the IRB. Renewal and completion forms are found on the web site under Forms and Templates.

**Adverse Event Reporting:** All unanticipated or serious adverse events must be reported to the IRB within ten working days.

**Modifications:** Prior IRB approval is required before implementing any changes in any of the approved documents. **Data cannot be used in the research if collected before any changes are approved.**

**Recordkeeping**: You must retain all signed consent forms for at least 3 years after all research activity is completed, including data analysis.

**Questions:** Please contact ORSP – Human and Animal Protections and the IRB at (415) 338-1093, or at protocol@sfsu.edu

Sincerely,

Institutional Review Board

**San Francisco State University 7/22/11**

**An Epidemiologic Health Study of Manganese Exposure in adult residents of**

**East Liverpool, Ohio**

**Researcher's Name: Rosemarie Bowler, Ph.D., M.P.H.**

**Department: Psychology**

## 1. STUDY AIM, BACKGROUND AND DESIGN

The proposed study aims to answer the following questions:

- Is there is a relationship between internal Mn levels in blood (Mn/B), toenails (Mn/T), and hair (Mn/H) compared to external Mn levels in air (Mn/air) and neuropsychological and neurological function in adults?

- Does the neuropsychological function of a group of Mn-exposed adults differ significantly with level of exposure in air?

### Exposure Background:

On November 16, 2010 the U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR) presented residents of the town of East Liverpool, adjacent to the Ohio River, with an air quality report describing the potential health risks from ambient metals. Analyses of the U.S. EPA's air monitoring data at three locations in East Liverpool have shown elevated ambient air levels of manganese (Mn) and chromium-III (CrIII) over a period of nine years and eight months (between January 1999 and September 2009). Mn-air levels in East Liverpool were found to be more than 50 times higher than those in another Mn-exposed Ohio town (Marietta), which, along with a similar non-industrially Mn-exposed town (Mt. Vernon), has been examined recently in a health study conducted by the P.I. and her colleagues. Ohio EPA identified the S.H. Bell Company, a facility that warehouses and packages primarily raw metals (including Mn) from all over the world, as an exposure source contributing to these elevated levels. The present study seeks a) to determine the possible health risks to residents of the high Mn-exposure in East Liverpool, and b) to compare any health effects to the towns (exposed and control) currently being studied by this team of investigators.

There is a time urgency to perform a health study of the Mn health risks in East Liverpool because the S.H. Bell Company has been required by Ohio EPA to reduce the community's exposure to Mn emissions. In two Ohio EPA and US EPA enforcement actions, the plant was asked to comply with the following guidelines in order to remain in operation: pave a dirt road on the State Line property, install a dust suppression program, enclose some storage piles, improve dust collection, and tarp all trucks leaving the S.H. Bell facility. The site upgrades

were completed in 2008 and it is anticipated that Mn/A will have decreased by the middle of 2011. Ohio EPA also plans to continue the air monitoring and, moreover, have already installed a $PM_{10}$ monitor and plan to install a $PM_{2.5}$ monitor which will assess the respirable fraction of the Mn particles.

The experienced research team proposing this health evaluation is prepared to conduct such a study of East Liverpool residents on short notice because they have already developed epidemiologic methods and applied them in the current health study being completed of the Mn-exposed town of Marietta, Ohio and the unexposed control town of Mt. Vernon, Ohio. Relevant health questionnaires - including questions on demographic and residential history, symptoms and illnesses, environmental risk characteristics, such as intake of Mn and iron in diet, time spent indoors and outdoors - have already been developed and tested and are appropriate for use in East Liverpool with minimal changes. Ohio Department of Health has pledged to assist the P.I. and study investigators with news media co-ordination and lending state-level support to the study team. Additionally, Dr. Michelle Colledge, who authored the East Liverpool Air Quality Report of November 16, 2010, will collaborate on the analyses of the air Mn exposure (ATSDR, 2010). Advanced staff members from the ATSDR and the U.S. and Region 5 EPA will collaborate with the team of investigators, trained neuropsychological testers, medical experts, and statisticians who have been working conjointly on the Marietta-Mt. Vernon study. They will be available this calendar year (2011) and are willing to work on the proposed on-site applied health research study in East Liverpool. The proposed study offers the opportunity to examine an additional, more highly Mn-exposed community, and to compare the results to the two towns in Ohio under current study.

**Exposure source:**

Ambient air monitoring has already been conducted at three monitor locations near the S.H. Bell Company in East Liverpool and ambient Mn-air measurements are available from the Ohio EPA and the ATSDR for a period of nine years and eight months.

As described in the East Liverpool Air Quality Report by the ATSDR of November 16, 2010 (ATSDR, 2010), the S.H. Bell Company handles a great volume of raw and processed metal products. S.H. Bell has two locations in East Liverpool, approximately one mile apart: the Little England facility and the State Line facility. Ferrous and nonferrous materials are stored, transferred, and warehoused at both locations. The S.H. Bell Company is equipped to process, dry, crush, screen, and package their ore/materials for industry. Shipping occurs through river barge, truck, and rail. On most days, this includes shipping out 1.5 barges and 100-120 trucks (ATSDR Health Consultation report, 2010). Although the company employed 52 persons in 2007, by 2009, this number decreased to 26 workers. The results of air monitoring reported in the November 2010 East Liverpool Air Quality Report showed highly elevated Mn levels in air (ATSDR, 2010). Only two metals, Mn and Cr were identified as elevated in the air sampled over nine years and eight months. More specifically, all of the identified chromium particulate matter was CrIII – no CrVI was noted. CrIII is not associated with an increased cancer risk and is not considered to be a health concern (ATSDR, 2010). The EPA's computation of a hazard quotient (HQ: ambient concentration divided by the reference concentration of 0.05 $\mu g/m^3$) of 30 indicated the residences near the Water Plant air monitor (S.H. Bell State Line facility) have the highest non-cancer risk, with 99% of the risk "attributed to Mn" (ATSDR, 2010).

The monitors located near the two S.H. Bell facilities in East Liverpool are (See Appendix A of this report and the Air Quality Report of November 16, 2010):

1. **Water Plant** monitor immediately adjacent to the S.H. Bell State Line facility. The air monitor is located approximately 250 feet W from the State Line facility with average Mn TSP concentration of 1.30 $\mu g/m^3$, range 0.10-23.0 $\mu g/m^3$

2. **Maryland Avenue** monitor located about 0.30 miles to the north-northwest of the S.H. Bell Little England facility – with average Mn TSP concentration of 0.18 $\mu g/m^3$, range 0.18-0.01-1.0 $\mu g/m^3$

3. **Port Authority** monitor located approximately 0.33 miles to the west-southwest of the S.H. Bell Little England facility with average Mn TSP concentrations of 0.26 $\mu g/m^3$, range 0.02-1.9 $\mu g/m^3$

Because the Water Plant monitor clearly shows the highest levels of Mn in air, the area around the water plant in a 1 mile radius will be the area studied under the proposed protocol. Additionally, census data indicates that this area has a sufficient number of housing units from which to recruit a random sample of 100.

The EPA has indicated that average Mn concentrations are between 0.04 and 0.05 $\mu g/m^3$ in urban areas. The ATSDR also reports average levels in urban areas of 0.05 $\mu g/m^3$ and the WHO reports concentrations near Mn sites to be 0.2 to 0.3$\mu g/m^3$ . The area around the East Liverpool air monitors is densely populated, making it an ideal natural laboratory to study the health effects of moderately high levels of Mn in air in an environmental setting.

**Human Exposure to Manganese:**

Manganese is a naturally occurring essential element and low levels of Mn in water, food, and air are ubiquitous. Although Mn is also contained in food, it is thought to be more readily absorbed from water and air. In certain geographic regions, long contact between groundwater and Mn in bedrock can lead to high levels of Mn in water (U.S.EPA, 2004). Industrial plants involved in the refining and processing of Mn ore have higher Mn emissions, which may affect the health of humans residing in close proximity. The Mn exposure route of most concern in the present study is inhalation, but blood biomarkers will reflect all routes of exposure. Diet will be surveyed with a suitable brief diet questionnaire to assess approximate intake of Mn rich foods such as nuts, beans and tea and whole grains (rice, wheat, oats, etc.), but diet is considered to have a minor contribution to adverse health effects. The proposed study will also provide pilot data that will subsequently help conducting an even larger, more comprehensive study by ATSDR at a later date. Funding by the US EPA of this study is presently pending the IRB approval at SFSU.

In the occupational health literature there are many reports of workers exposed to Mn with adverse health effects. Miners and chemical workers who are over-exposed to Mn, a major component in iron/steel welding fumes, are known to be at risk for developing a pattern

of signs and symptoms showing a decline in psychiatric health (i.e. mood disturbance) and cognitive ability (i.e. problems with attention, memory, and information processing) and a movement disorder similar to Parkinson's disease (PD) (i.e. a disturbance of gait, loss of balance, dystonia, bradykinesia, and tremor) (Bowler et al., 2007).

Environmental studies of airborne Mn have been relatively rare and results of a select few studies have been published. At the first major conference on the effects of long-term, low-level exposure to Mn in Little Rock, Arkansas in 1997, an inter-disciplinary international forum was held on state of the art research data on this issue, which was followed by publication of the peer-reviewed papers presented at that time. In this special April/June 1999 issue of the Journal of NeuroToxicology only 7 out of 33 published papers reported on environmental human exposure to Mn, including exposure to Methylcyclopentadienyl Manganese Tricarbonyl (MMT) (2 publications) and the neuropsychological effects of environmental Mn exposure (5 publications). Lynam et al. (1999) reported no effects of MMT and of ambient air levels of car emissions in Toronto, Canada. Zayed et al. (1999) also reported a lack of effects of potential exposure to MMT in residents near a gas station and underground parking garage, but did report "substantial concentrations of respirable Manganese ($Mn_R$)".

Neuropsychological effects of environmental Mn exposure were reported by Mergler et al. (1999) in their study of 273 community residents in Quebec, Canada, for whom a relationship of lower neuropsychological function with higher Mn in blood was found. Higher levels of Mn were also shown to be associated with changes in coordinated upper limb movements and poorer learning and recall. An interaction between Mn and increasing age (>50) was found for motor tasks. Bowler et al. (1999) reviewed the literature on neuropsychiatric effects of Mn on mood and described these effects in the group of 273 community residents in Quebec. These effects were categorized to be anxiety, psychotic experiences, emotional disturbance, fatigue, compulsive behaviors and aggression and hostility. Baldwin et al. (1999) described the bioindicators and exposure data of the Mergler et al. (1999) study and reported air samples of total particulates measured from 4 sites were between 0.009 $\mu g/m^3$ and 0.035 $\mu g/m^3$. These levels of Mn in air are considerably lower than those in East Liverpool.

Studies by Lucchini et al. (2007) report an increased prevalence of Parkinsonian disorders associated with Mn exposure in the vicinities of ferroalloy industries in Northern Italy. Concentrations of Mn in settled dust measured in 206 municipalities were significantly higher near and downwind from two of four industrial plants. Near one of the four plants studied, airborne concentration of Mn in total dust averaged 300+ 533 $\mu g/m^3$ (range 20-1600). The estimated range of ultrafine $PM_{2.5}$ particles in six locations, within a distance of about 2 km from plant B (Lucchini et al., 2003) were also measured outside the plants in 2001 and showed a geometric mean of 0.69 $\mu g/m^3$ (range 0.2-1.8). The respirable fraction of Mn was reported to be 25% to 90% of the total dust from the plants.

In 2007, Finkelstein and Jerrett (2007) re-visited the concerns over industrial emissions due to MMT and investigated an association of PD and Mn exposure in a cohort of 110,000 subjects in Toronto and Hamilton, Canada. They used residential postal codes and did geocoding to assign longitude and latitude coordinates for each resident. Thus, the residential locations were analyzed for distance from a major urban road. Hamilton residents were

exposed to both mobile sources of MMT and industrial Mn emissions from steelmaking industry, while residents in Toronto were without "substantial" industrial emissions of Mn. Manganese in total suspended particulate in Hamilton (TSP were 50.5, to 92.1 ng/$m^3$ ) was found to be significantly higher than in Toronto (9 ng/$m^3$). Results of the prevalence curves for PD indicated that ambient exposure to Mn results in diagnoses of PD at an earlier age, which was postulated to be consistent with the theory that increased Mn exposure is associated with increased neuronal loss in the aging process.

Although few comprehensive studies of environmental exposure to Mn have been reported, a small body of recent research has associated Mn exposure with learning and neuropsychological deficits in elementary school children. Wasserman et al. (2006) reported dose-effect relationship between concentration of Mn in drinking water and decreased IQ. Likewise, Chinese investigators reported that scores on tests of learning and neuropsychological functions were lower in elementary school children exposed to Mn in drinking water (MnW) at levels of 241-346 ug/l than in children from a control group with very low Mn levels in drinking water. Levels of Mn in hair correlated with several neuropsychological scores. Additionally Zhang et al. (1995) reported lower levels of serum 5-hydroxytryptamine (5-HT), dopamine, norepinephrine and acetylcholine esterase in the exposed children. Bouchard et al. (2007) reported a significant relation between levels of Mn in water and hair of children as well as an increase in indicators of hyperactive behaviors with Mn in hair.

In conclusion, although the recent studies on children show decrements in neuropsychological performance, none of these recent environmental studies on adults included comprehensive neuropsychological function with air measurements, such as those refined and detailed in East Liverpool air reports. Only the earlier work by Mergler et al. (1999) related Mn in air to neuropsychological function. This present study seeks to fill that gap and will utilize past knowledge gained from these studies by using a more refined and recently updated neuropsychological test battery, including the Computerized Adaptive Testing System (CATSYS) to assess tremor and sway, in addition to geo-coded data in relation to the refined air modeling results already performed by ATSDR and EPA in Marietta.

## BACKGROUND

Air monitoring at the three locations near the S.H. Bell Company in East Liverpool has already been conducted by the Ohio EPA and the ATSDR over a period of over 9 years. This proposed project is to be conducted with a randomly selected sample of adult residents aged 30-75 years (under a contract between SFSU and the US EPA with partial in-kind contributions of personnel from the ATSDR and EPA). Randomly selected study participants will include 100 residents, selected from property tax records in East Liverpool, OH, within a parameter of 1 mile from the Water Plant air monitor. This study will include neurological and neuropsychological evaluations and measures of Mn exposure in air and levels of Mn biomarkers measured in blood, hair, and toenails. Upon completion, this study will contribute knowledge about the potential risk for health effects associated with the higher ambient Mn air measured in East Liverpool.

East Liverpool has 13,089 residents and is similar in size to the two towns (Marietta: 14,515 residents and Mt. Vernon: 14,375 residents) currently being studied by the investigators

(see Appendix C). East Liverpool is also similar to these two towns in ethnic and gender proportions, median age, and income; however, the percentage of residents living below poverty in East Liverpool is lower than in Marietta and Mt. Vernon. The percent of residents having less than a high school education in East Liverpool (26.6%) is higher than in Marietta (15.9%) and Mt. Vernon (19.8%) and fewer residents of East Liverpool are college graduates or have post-graduate degrees. Both Mn-exposed towns, Marietta and East Liverpool, are situated on the Ohio River and both have Mn polluting industries near the city. Both Marietta and East Liverpool have industrial plants with documented chemical emissions, with Mn being the pollutant of greatest concern. The exposed town of Marietta has an industrial complex with a ferroalloys facility, Eramet, being the main point source for Mn emissions. Mn air emissions in Marietta have been shown to range from 0.01 to a maximum concentration of 0.5 $\mu g/m^3$; while East Liverpool, the proposed more highly exposed town, has Mn maximum concentrations 50 times higher than in Marietta (25.0 $\mu g/m^3$). Mn exposure for Mt. Vernon was considered to be low based on data from the Toxic Release Inventory, and the town was therefore selected as a comparison/control town.

- **Study Design:** The proposed health study will utilize a cross-sectional design using a Mn-exposed group of 100 residents of East Liverpool drawn at random as an add-on to the 100 exposed residents from Marietta and 90 control residents from Mt. Vernon, who are part of a study currently being completed. The same age group (30-75 years of age), which was used in the prior study of the first two towns, and the same methods of selection/recruitment, inclusion and exclusion criteria, and neurological and neuropsychological test measures and procedures will be used in this current study of East Liverpool, Ohio. This study conducted in Marietta and Mt. Vernon, had received IRB approval from both SFSU and the Ohio Department of Health (ODH).

- **Data collection methods:** The same carefully controlled and standardized test administration instructions as those used in the Marietta/Mt Vernon study will be applied to the data collection procedures in East Liverpool. To the extent possible, the testers will be the same as in the initial study. The test battery and test description are listed in Appendix B. All final questionnaires are also submitted to the IRB for approval. Additionally, an IRB protocol will be submitted by the US EPA, who have contracted the University of North Carolina to conduct their IRB reviews.

The data collected in this study will include the following:

1. Air exposure of Mn, already collected by the ATSDR for the period between 1999 and 2009 (9 years and 8 months).

2. Neuropsychological (including mood and motor efficiency) tests (Appendix B)

3. Neurological function will be assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) administered by the same trained physician (2 subscales: Activities of Daily Living and Motor Function)

4. The CATSYS (Danish Product Development) will also be administered by the same doctoral level examiner as prior – consisting of 4 postural sway conditions and hand tremor.

5. A health questionnaire containing sections on residency, symptoms, medical history, medications, work history and behaviors, diet, and personal demographic information.

6. The possibility of worry impacting symptom reporting in the East Liverpool group will be addressed in two ways: A) we will include an Environmental Worry Scale (EWS, enclosed), scores of which will be analyzed as a potential confounder and B) all examiners will be (most already are) trained in detecting symptom and cognitive impairment exaggeration. Additionally, a short test of effort (Rey-15) will be administered, which if failed, will result in the administration of a highly regarded test of symptom validity, the Victoria Symptom Validity Test (VSVT). This test is designed to provide evidence that can confirm or disconfirm the validity of an examinee's cognitive and symptom impairments. In the event that the examinee fails both the Rey 15 and the VSVT, that participant's test scores will be excluded from the group analysis.

7. Whole blood will be analyzed for levels of manganese (Mn), mercury (Hg), cadmium (Cd), and lead (Pb). Toenail and hair samples will be analyzed for levels of Mn. One additional tube of whole blood drawn for each participant will be centrifuged to derive ferritin in serum (Ferr-Serum) which will be used for testing iron store. In total, 12 mL whole blood will be collected from each participant for analyses. All blood and serum samples will be shipped on dry ice by Fed Ex immediately to the CDC and EPA laboratories. The samples will be identified by each participant's ID number only and no names will be included. The P.I. will hand-carry the list identifying the participants' names and ID numbers.

The ATSDR, represented by Dr. Michelle Colledge and Ms. Stephanie Davis, will be collaborators on the proposed project to assist on the analysis of the monitoring data from the East Liverpool region. Dr. Danelle Lobdell, an epidemiologist from the U.S. EPA National Health and Environmental Effects Research Laboratory, Human Studies Division, will serve as the Technical Consultant on the project. The data of Mn in air collected over the 9 years and 8 months and published in the November 2010 Health Consultation report, will be the basis for determining external Mn exposure. Additionally, internal exposure will be assessed through blood, hair, and toenail analyses for the presence of Mn in the body. The neuropsychological test performance data will enable the comparison of the East Liverpool group's motor efficiency, movement, cognitive level and their function on postural sway and tremor with that of the Marietta and Mt. Vernon groups and with established normative data. The information collected from the medical, social, and psychological history questionnaire will be used to control for factors (other than exposure to Mn) that could affect an individual's test performance. The use of standardized and well-recognized tests will also allow us to examine

the neuropsychological test performance data in relation to the exposure data (both internal and external) to determine the presence of dose-dependent differences in neuropsychological function.

- **NEUROPSYCHOLOGICAL TESTS AND DESCRIPTIONS**
  The test battery and test descriptions are listed in Appendix B.

- **Data Analysis Plan**

In order to compare scores on neuropsychological, motor and mood tests, and the UPDRS between the three towns, the general linear model will be used. This will test for differences between participants in the three towns, including pairwise comparisons for differences in domains of neurological, neuropsychological, mood and motor functioning, with covariates included in the model as necessary. Logistic regressions will be used for dichotomous outcomes such as symptom and illness frequencies in each town, comparing the relative risk between the samples after controlling for the effects of covariates.

Multiple regression analyses will test for relationships between Mn levels in air, blood, hair, and toenails, and neuropsychological test scores in East Liverpool, and these relationships will be compared to the results recently obtained in Marietta. Logistic regressions will be used for categorical outcomes to examine the relationship between Mn levels in air and risk for particular illnesses or symptoms and mood.

Power analyses using G*Power statistical software indicated adequate statistical sensitivity with a sample size of 100. Setting power at 0.80 and alpha at 0.05, one-way between groups analyses of means would be powered to detect an effect size of f=.18 or greater. This is halfway between a small and medium effect size based on Cohen's (1988) guidelines, and should be sufficiently sensitive to detect the effects of manganese exposure in this sample, based on theory and previous research.

- **Limitations of the available Exposure Estimates**

The current proposal does not include individual quantitative estimates of actual air Mn exposures but the monthly averages of Mn in air monitored in the area studied will be used to model exposure. Questionnaires and biomarker results will be used to help rule out confounding exposure from other chemicals analyzed in blood and serum. The understanding is that the current proposal's "exposure assessment" includes only one group of East Liverpool participants residing within one mile of the Water Plant air monitor who have 50 x greater airborne Mn exposure than residents in Marietta and the comparison residents of Mt. Vernon. The basis for this exposure assumption is described above. Dietary information of foods containing Mn, Mn in diet supplements, and Mn in blood, hair, and toenails will be collected and analyzed with the functional variables assessing possible dose-effects. This study is supplemental to the pilot study for the larger proposed ATSDR study and has a narrow focus on neurobehavioral and health outcomes in relation to Mn in ambient air, blood, hair, and toenails, with diet as an additional surrogate for Mn.

- **Significance:**

1. This study will contribute to the knowledge of effects of environmental exposure at different levels to airborne Mn on neurological and neuropsychological functions of randomly selected adults.
2. Although Mn exposure has been reported in numerous studies of occupational workers, very few reports of environmental Mn exposure are available. This study will add to the findings of the Marietta study by investigating a highly exposed town, which will contribute to
    - knowledge about environmental Mn data in air and in blood, hair, and toenails, and the level of exposure that may be related to developing symptoms related to Mn exposure
    - knowledge of the relationship of Mn in air to neurological neuropsychological and health status
    - addressing concerns about potential health effects in the exposed town of East Liverpool when comparing the adult test data to that of Marietta and Mt. Vernon and to normative ranges of unexposed populations
    - piloting and refining the study methodology for a larger study being planned by the ATSDR

## 2. PARTICIPANT POPULATION

**a. Participants:** The proposed health study will recruit 100 individuals residing within one mile of the Water Plant air monitor in East Liverpool, Ohio. Due to the similarities between East Liverpool and the two communities already studied, the selected participants are expected to be similar on age, gender, ethnicity, and level of education (Appendix C).

**b. Inclusion criteria**

To be included in the study, participants must be 30-75 years old and have 10 years or more of residency in East Liverpool. Participants must live in homes serviced by the municipal water supply and must reside within one mile of the Water Plant air monitor in East Liverpool, Ohio.

**c. Exclusion criteria**

1. having had a major occupational exposure to pesticides, fungicides, or herbicides, carbon monoxide (CO), or other heavy metals requiring a medical visit

2. a diagnosis of a psychiatric, neurological, or hepatic medical condition, including: stroke, electroconvulsive treatment, epilepsy, brain surgery, encephalitis, meningitis, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's dementia, schizophrenia, bipolar disorder

3. current treatment for alcohol or drug dependence

4. prior head injury or a stroke resulting in hospitalization for more than 1 day

5. having worked at S.H. Bell at any time

6. women who are pregnant or nursing

**RECRUITMENT**

Participant recruitment will be preceded by public announcements of the study. The study announcement will be made in East Liverpool after EPA's final approval of funding toward the end of May or beginning of June, 2011. The recruitment plan is outlined below.

**a) Community Meetings and Health Study Announcements**

1. Community meeting announcements will be made via radio, newspaper, and television. Letters to a random sample of the East Liverpool households within 1 mile of the Water Plant monitor. It will include a stamped, self-addressed postcard where residents will be able to indicate their interest in study participation if they are eligible (determined by a phone call interview).

2. The study P.I. and her assistant will travel to East Liverpool on the third Thursday of the chosen month (August 2011) to meet with the Health Commissioner and her board, presenting the study. The following evening, a meeting for the community will be held to describe the study as outlined below in # 3.

3. The community meeting in East Liverpool will consist of a presentation of a brief slide show (revised for East Liverpool, with the prior slides for the Marietta, Ohio study already approved by SFSU) detailing the description of the study to all of the interested residents and stake holders (Ohio Department of Health, Ohio EPA, resident groups, health department officials, etc.) and the U.S.EPA and ATSDR.

**b) Recruitment Procedure:**

The sample of households in the area of 1 mile surrounding the East Liverpool Water Plant air monitor and S.H. Bell will be obtained from a property tax database. Residential addresses will then be plotted in county geographic information system (GIS) databases to ensure that they fall within the desired area of study of within one mile of the Water Plant monitor. Ms. Stephanie Davis from the ATSDR will assist in in this process.

1. At least 5x the number of needed addresses will be chosen at random from the GIS database and letters containing the recruitment materials will be sent, which will include a self-addressed, stamped card which could be used to indicate willingness to participate or denial to participate in the health study. If participants indicated interest, a brief questionnaire listing the exclusion factors will be administered during telephone calls to the participants. If the number of return cards received 2 weeks after the mail out is insufficient, the research team will attempt to contact potential participants via telephone. In an attempt to reach potential participants, a maximum of three phone calls will be made to those who have an answering machine and a maximum of five phone calls for those who

do not have an answering machine. The telephone numbers will be obtained from an East Liverpool telephone book. If the responses are insufficient in number, this process will be repeated until 120 adults are available to be tested or until the maximum number of phone calls has been reached for each potential participant (20 alternates are included to be called if any of the first 100 participants cannot come in the last few days prior to the appointment).

2. Calls will be made until 120 individuals agree to participate.

3. Selected participants will be contacted by telephone 4 weeks prior to the study to set up appointments at a convenient location.

4. Two days prior to the appointment, telephone appointment reminder calls will be made.

5. Because of concern and interest about chemical exposure, a relatively high response rate of ~50% is expected in East Liverpool.

**STUDY PROCEDURES**

**1.** The above recruitment methods will be followed.

**2.** Examiners will meet the day prior to testing and set up testing areas, review all test administrations and set up stations and offices where consent forms, interviews, and tests will be administered.

**3.** At the time the study will begin, scheduled study participants in groups (three groups per day) of 11 people (+ 1 extra person on one of the days) will be seated in a common area and greeted by the P.I. who will give a brief introduction about the study, the procedures, and the consent form.

**4.** The P.I. will interview all of the participants with a brief, somewhat structured interview schedule, asking participants about special concerns, fears and observations related to their exposure. The check-out staff person will at this time collect and de-identify the participant's list of current medications, (copied each night at the conclusions of testing) which will be hand-carried in carry-on luggage by the P.I.

**5.** Trained examiners will introduce themselves to participants and will explain the consent form in detail. Participants will be given time to ask questions. Then two copies of the informed consent will be signed; one for the participant and one for the researcher.

**6.** The participant will be invited to accompany one of the testers to a private room for testing. The neuropsychological testing will be conducted without any identifiers on the test protocols other than the respective I.D. number. Examiners will be two

neuropsychologists and six graduate students in psychology, who will be trained by the P.I. and senior staff (all have completed the course for the protection of human subjects – certificates attached to this protocol).

**7.** After completion of the tests, the study staff will introduce participants to the certified phlebotomist, who will draw a total of 12 mL of venous blood from each participant for analysis. The Centers for Disease Control and Prevention (CDC) Environmental Health Laboratory has agreed to perform the blood analyses of whole blood for Mn, Pb, Cd, and Hg levels, as well as the serum ferritin levels. A total of 200 samples (two vials per participant, 6 mL each) of whole blood will be collected from study participants by the licensed and trained phlebotomist/medical technician. Presumably, one needle stick per participant (or as few as needed) will be used by the certified phlebotomist/medical technician. Four mL of whole blood will then be centrifuged at 800 x g for 10 min at room temperature to separate the serum. Whole blood and serum samples will be immediately stored at -40°C until analysis and sent weekly by Express Mail to the laboratory. Half a milliliter of serum is needed for the analysis of ferritin concentrations by immunoturbidity using the Roche Tina-quant assay on the Hitachi 912 clinical analyzer. The usual QA/QC methods of the CDC Laboratory will be applied. Each analytic run is surrounded by at least two levels of bench quality control and one blind quality control sample is inserted with each run (40-60 samples). The methods are CLIA-certified and multiple PT are run, as available. The DLS QA/QC system (Caudill et al., 2008) is referred to as the Multi-Rule Quality Control System (MRQCS). The CDC rules are similar in nomenclature to Westgard's format, but the rules are not identical. Some of the additional features of MRQCS include the ability to distinguish between within-run and among-run precision, accommodating variable numbers of QC measurements per run and accommodating variable numbers of QC samples per pool. Quality control measures include analysis of initial calibration verification standard (National Institute of Standard and Technology standard reference material (NIST SRM) 1643e (trace elements in water, Gaithersburg, MD), a solution of NIST traceable 1 ng $ml^{-1}$ manganese standard as the continuous calibration verification standard, procedural blank and Certified Reference material GBW 07601 (human hair) (Institute of Geophysical and Geochemical Exploration, Langfang, China) will be used as the quality control sample. Results will be given as the average of five replicate measurements of the instrument. Recovery of the analysis of QC standard by this procedure is 90% -110% and, precision is given as %RSD (SD*100/Mean) and for hair samples it varied from 1%-25%.

**8.** Hair samples will be collected using the following procedures: The collector will first evaluate the presence of sufficient hair on head for collection. Approx. 1-3 cm of hair should be available for collection. The scissors will be cleaned with an alcohol swab in front of the participant. Hair will be cut as close to the skull as possible from the base of the skull near the point halfway between the spine & ear (lower right or left quadrant). When enough mass is an issue, typically on men, smaller snips of hair will be taken in a random pattern. The side of hair sample that was close to the scalp will be marked by

tying that end off with sewing thread and the collected hair will be placed into a small plastic bag with the participant's id clearly indicated on the bag. All small bags will be sealed and placed into a container and sent to the laboratory for analysis.

**9.** Toenail samples will be collected in the following manner: A pair of titanium dioxide nail clippers will be rubbed with alcohol swabs to be thoroughly cleaned between people. Participants will be asked to clip their nails from all ten toes onto a clean paper (to make it easier to catch all the clippings) and place the collected nails in a small plastic bag labeled with their respective ID. All small bags will be placed into a container and send to the laboratory for analysis.

Whole sample (Hair/Toenails) will be pre-cleaned with 1% Triton X-100 solution prior to analysis to remove extraneous contaminants. Samples will be acid digested using ultra pure nitric acid at room temperature for 24 hours. Diluted samples will be analyzed for manganese using inductively coupled plasma mass spectrometry (ICP-MS, DRC-II, Perkin Elmer, Norwark, CT) using indium as the internal standard.

**10.** Two post-baccalaureate level students who were also part of the testing team in Marietta and Mt. Vernon, OH, will conduct check-in and check-out and review the questionnaires and individual participant folders to ascertain that all tests have been completed before the participant leaves. This protocol completeness review will be performed in order to detect unintentional omissions. Participants will at no time be pressured to answer any items they choose not to answer.

**11.** Upon completion of the study, a gift card for $50.00 for a local store will be presented to each participant as a token of appreciation for participation in the study.

**12.** Feedback of the group's results will be given to the community and all interested parties either in person or in written form during late summer of 2012. If additional funding becomes available, the P.I. will also present group results of the study in a community meeting in East Liverpool.

**13.** After the conclusion of the study, a brief feedback report will be prepared and mailed to each participant reporting the individual's test scores (by domain of function) and results of biomarker analyses. This report will also indicate whether the test results were:

a. within the normal range
b. of concern, needing a referral to the family physician for further assessment by specialists as indicated.

**14.** All relevant professional parties and city officials will be contacted and given feedback of the group's findings.

**15.** All inquiries by the media will be answered by the team of investigators including the P.I. and Ms. Stephanie Davis, representing ATSDR. Prior to any release of data, results and talking points will have been presented to the entire group of investigators, collaborators and advisory board for input and final wording.

**Research details**

- The proposed study will take place in rented facilities at locations convenient for participants in East Liverpool, Ohio. The P.I. will select the facilities and will make sure that they offer the privacy needed for conducting the study procedures.
- Each participant will be engaged in the study procedures for an average of 2.5 to 4.0 hours.
- It is expected that the brief introduction to the study by the P.I. and consent procedure will take no longer than 10 minutes since participants will already have received detailed information in the recruitment letters. Participants will be engaged in filling out questionnaires for approximately 50 minutes, following which they will have a brief interview by the P.I. for about 10 minutes. The administration of the neuropsychological test battery is expected to take approximately 90 minutes. The administration of the CATSYS is expected to take 10 minutes. The neurological examination (UPDRS) will last 15 minutes. Participants will then have refreshments for about 10 minutes before being introduced to the certified phlebotomist for the drawing of the blood and hair sample collection, followed by the collection of toenail clippings by participants, which will each take 10 minutes.

**4. RESEARCH RISKS**

- Drawing venous blood from the arm may cause minimal pain when the needle is inserted. There is also a slight risk of bruising and infection where the needle punctures the skin. In rare cases, some people may experience lightheadedness, nausea, or fainting. The certified phlebotomist is trained in recognizing and dealing with these types of reactions. All possible accommodations will be made should this occur. Cutting a small amount of hair will be done with a blunted scissors which will prevent any accidental injuries. Blood samples will also be marked with an ID number only to ensure those analyzing the blood are blinded to the identity of the participant. Arrangements will be made with a local physician on call, who will be recruited by a local colleague practicing in East Liverpool. The pager number and location of this local physician will be obtained so he/she may be contacted and available to address any medical emergency that may arise. Although such emergencies are highly unlikely, a participant, if necessary can be brought to the nearest Emergency Room at the local hospital.
- There is a risk of experiencing slight fatigue during testing. Testers are trained to look for signs of fatigue and a break will promptly be offered. The participants will also be informed that they can take a break or discontinue testing at any point.

- Participation may involve potential loss of privacy. To minimize this, results will be stored in a password-protected computer database with no identifying information attached. Hard copy files of all of the data will be kept by the P.I. in a locked file cabinet for 5 years with documents containing ID numbers only. Any documents or computer files linking ID numbers to names will be kept in a separate, locked file cabinet (or computer database) only accessible by the P.I. and will also be destroyed after 5 years.

**5. CONFIDENTIALITY**

All test results will be linked to an ID number, with all personally identifying participant information removed. Results will be stored in an encrypted document on a password-protected computer and all paper materials will be stored in a locked file cabinet in Dr. Bowler's research office laboratory at 8371 Kent Drive, El Cerrito, CA 94530. Only Dr. Bowler will have access to information linking ID numbers and the identities of the participants. Each page in the participant's folder will be coded with an ID number only.

Security will be maintained by having an alarm system in the building and by having each staff member sign a special Data Contract to maintain confidentiality of the data, refraining from any public conversations about the participants. The data will not be released unless subpoenaed by a court of law. Anyone working on the data will also be required to sign this, guaranteeing confidentiality and guaranteeing that these data will not be used unless the P.I. is involved in order to guarantee privacy to the information given by the participant. All data will be maintained for approximately 5 years in hard copy, limiting access to only authorized individuals. The electronic data will be securely stored indefinitely. Unauthorized access will be reported to the relevant parties (IRB, participants, stakeholders). Electronic data will be saved on a device that has the appropriate security safeguards, such as unique identification of authorized users, password protection, automated operating system patch (bug fix) management, anti-virus controls, firewall configuration, and scheduled and automatic backups to protect against data loss.

**6. BENEFITS**

There are no direct benefits to participants.

**7. PAYMENT**

Upon completion of the study, a gift card for $50.00 from a local store will be presented to each participant as a token of appreciation for participation in the study.

**8. COSTS**

There is no cost for taking part in the study, aside from the transportation costs of coming to the appointment. Transportation costs involved in coming to the facility, which will be selected to be convenient for participants, will not be reimbursed. The researchers, research team and sponsors of this project will not provide medical care nor cover the cost of medical care for participants.

**9. ALTERNATIVES**

The alternative is not to participate in the research.

**10. CONSENT/ASSENT PROCESS AND DOCUMENTATION OF CONSENT**

**a.** The study will first be introduced to East Liverpool residents at the community meeting that will take place in July or August 2011, after funding approval is received. A slide show detailing the study procedures for the community residents and a handout describing the upcoming health study will be distributed at the meetings. Residents will be informed that they might receive a letter from the P.I. containing the study description. If selected, residents will be asked to complete and return a stamped, self-addressed card indicating willingness or non-willingness to participate to the P.I. Participants will be able to have their questions answered during the recruitment and screening calls, as well as later, at the time of the appointment. They will be able to ask the P.I. any additional questions that may arise either on site after the meeting or over the telephone when they are administered the inclusion/exclusion questionnaire. They also will be provided additional time to ask questions when the IRB approved consent forms are explained and reviewed by the examiners with each participant at the time of testing. The consent forms will be kept in each participant's testing protocol folder for the duration of the study procedure. Upon arrival at the P.I.'s office, the consent forms will be removed from the folders containing the participants' test protocols and will be in possession of the P.I. , along with the list connecting IDs and names. These forms will be kept in a locked file cabinet in the P.I.'s office.

**b.** Participants will receive a signed copy of the consent forms.

**c.** Additionally, the standard HIPAA consent form will be used in case clinical issues arise.

**11. INVESTIGATORS' QUALIFICATIONS**

a. **Professor Rosemarie Bowler** is a licensed neuropsychologist, qualified medical evaluator, and an emerita lecturer at SFSU. She has published numerous research articles on neurotoxicants and their effects on health. She has previously been on the committee at the National Academy of Science, Institute of Medicine and has served on the CDC/ATSDR Board of Scientific Counselors. She has taught at SFSU since 1977, recently retired, but is still teaching, training and supervising SFSU Psychology graduate students, as well as Ph.D. students in other universities. Professor Bowler has conducted numerous studies of neurotoxicity in adults and has also been responsible for 5 major epidemiologic studies of the effect of neurotoxicants on children (in California, Ohio, France and New Mexico). She has served on numerous committees and boards regarding the chemical effects of exposures on human populations.

**Dr. Harry Roels,** Université Catholique de Louvain (UCL), Brussels, Belgium. Professor Roels has a long history of scientific work with human populations exposed to neurotoxicants. Professor Roels is one of the most well-known scientific experts on Mn, in fact his study of battery workers in Belgium resulted in the lowering of the Threshold Limit Values (TLVs) of Mn. Dr. Roels is a sought out international expert on Mn and is on many international federal

committees on scientific issues related to Mn. He will work closely with the P.I. on all neurotoxicologic and epidemiologic areas of the study.

**Dr. Yangho Kim**-Department of Occupational and Environmental Medicine, Ulsan University Hospital, College of Medicine, South Korea

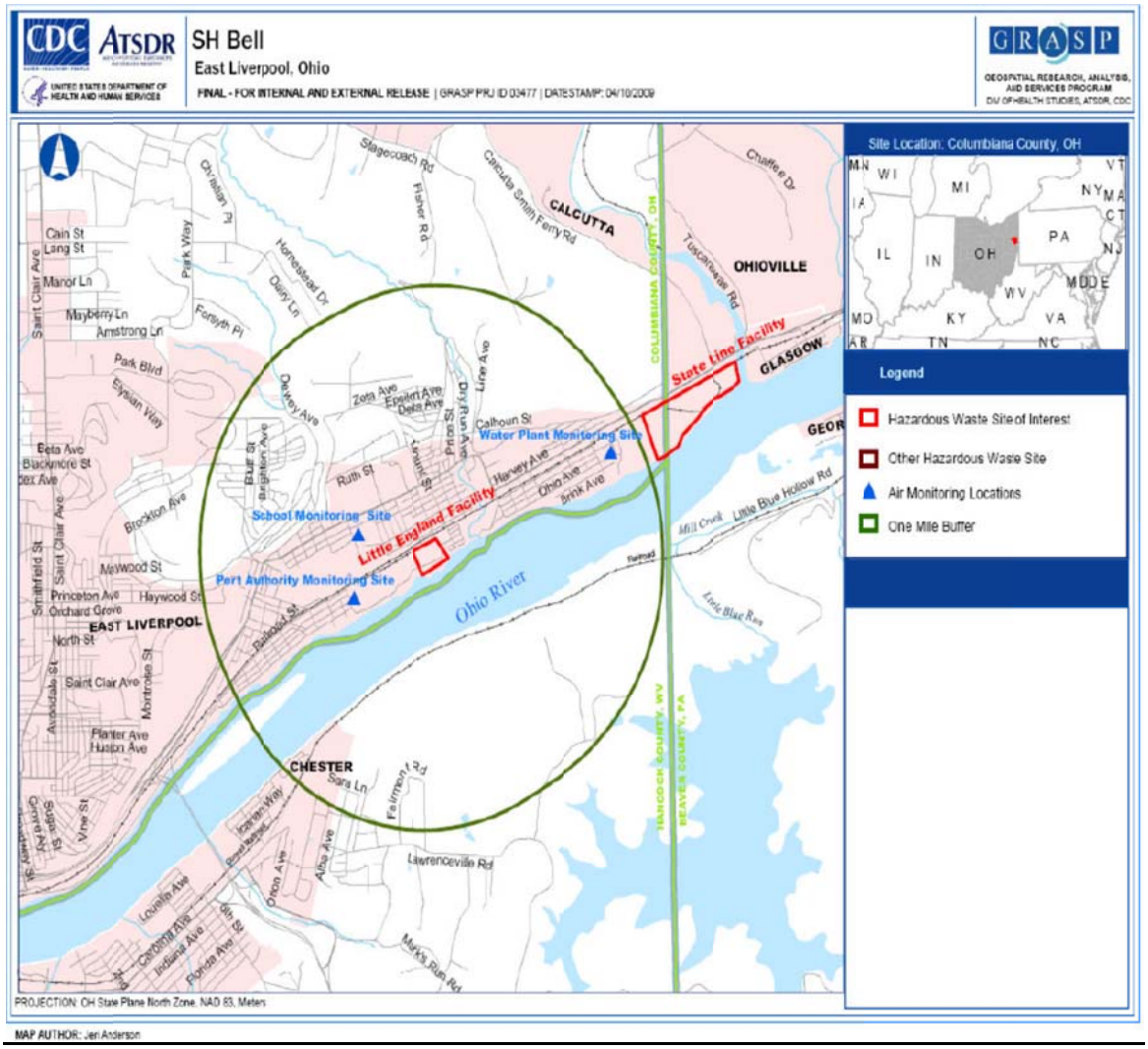
**Dr. Long Ngo**-Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts. Dr. Ngo is an Assistant Professor of Medicine (biostatistics) at Harvard Medical School. He has collaborated with the P.I. on several other studies and has experience in constructing and analyzing exposure models.

**Trained examiners/psychometricians:**
**Dr. Stephen Rauch,** San Francisco State University, Department of Psychology
**Vihra Gocheva, MA** (pending, San Francisco State University)
**Matthew Harris, MA, Ph.D.** (pending, Alliant International University)
**Linda Mora, MA, Ph.D.,** Oakland Children's Hospital
**Katherine Wilson, MA, Ph.D.** (pending, Alliant International University)
**Beth Stutzman, MA, Psy.D.** (pending, The Wright Institute)
**Matthew Beristianos, MA, Ph.D.** (pending, Alliant International University)
**Matthew Leonard, MA** (pending, San Francisco State University)
**Ralph Rasalan, MA** (pending, San Francisco State University)
**Nadia Abdelouahab, PhD,** University of Sherbrook, Montreal, Canada
2 trained psychology students-TBA
1-2 additional trained data-entry persons from psychology research classes at SFSU

## 12. FUNDING SOURCES

Funding by the USEPA is pending. The US EPA will award funding of this study as a Co-Operative Agreement and both institutions (USEPA and SFSU) have already begun to set up the process of transferring funds. The study will commence immediately once final approval is given, and testing is hoped to begin in September 2011. The main contact person responsible for communication of the cooperative agreement at this time at the U.S. EPA is Dr. Danelle Lobdell at the National Health and Environmental Effects Research Laboratory in Chapel Hill, NC. The contact person for EPA at Region 5 is Dr. George Bollweg. Funds will be processed through the Office of Research and Sponsored
Programs (ORSP) at SFSU. No conflict of interest exists for any of the researchers.

## Appendix A. East Liverpool Area Map in Relation to the 3 Air Monitor Sites



## Appendix B. East Liverpool Test Battery

### I. NEUROPSYCHOLOGICAL BATTERY (120 MIN)

A. Cognitive (90 min):

1. Animal Naming
2. Digit Symbol Coding
3. Rey-O Copy
4. Digit Span
5. Rey-O Immediate
6. ACT
7. Stroop Color Word Test
8. Trails A & B
9. Similarities
10. Rey-O delayed
11. NAB Memory
12. REY-15
13. Victoria Symptom Validity (if needed, based on Rey-15 scores)

B. Motor & Tremor :

- CATSYS
- Grooved Pegboard
- Fingertapping
- Dynamometer
- Parallel lines

C. UPDRS – ADL and Motor (15 minutes)

D. Mood:

- SCL 90-R
- BRFSS
- Satisfaction with life Scale
- Environmental Worry Scale (EWS)

### II. SELF-REPORT QUESTIONNAIRES

- Health Questionnaire

### III. BIOMARKERS & AIR MEASUREMENTS

A. Blood:

- Mn, Pb, Hg, Cd

B. Hair
   Mn

C. Toenails:
   - Mn -10 toenail clippings

D. Serum:
   - Ferritin

**Test Battery Details**

**Cognitive Tests** *(In alphabetical order)*

***Animal Naming*** (Lezak et al., 2004)*:*

A category fluency test, requiring the naming of as many animals as possible in 1 minute.

***Auditory Consonant Trigrams (ACT)*** (Lezak et al., 2004):

A test of divided attention and concentration in which participants are orally presented with 3 consonant letters and a specified number from which they are asked to count backwards by three for 3, 9, or 18 seconds, at which point counting is interrupted and they have to recall the 3 consonants.

***Neuropsychological Assessment Battery (NAB): Memory Module*** (Stern and White, 2003):

A test with high ecological validity consisting of an array of subtests assessing learning and memory. Subtests include: list learning, shape learning, story learning and daily living memory with immediate and delayed recognition trials and forced-choice recognition.

***Rey-Osterrieth Complex Figure Test*** (Meyers and Meyers, 1995)*:*

Assesses planning, organizational skills and problem-solving strategies and perceptual, motor and memory functions. To assess visuospatial constructional ability and visuospatial memory participants are asked to copy a complex figure and then to reproduce it after a 3 and 30 minute delay. It has been shown sensitive in Parkinson's disease and frontal lobe damage.

***Stroop Color and Word Test*** (Golden, 1978)*:*

Measures the ease with which a person can shift his/her perceptual set to conform to changing demands and suppress a habitual response in favor of an unusual one. The test involves word reading, color naming, and set shifting (reading color names printed in a different color ink) and is sensitive to dementia, depression, PD, schizophrenia, Huntigton's disease, and head injury. Color-blind subjects are excluded.

***Trail Making Tests (TMT)*** (Strauss et al., 2006)*:*

Tests of speed of attention, sequencing, mental flexibility, visual search and motor function. It requires connecting in order encircled numbers or letters, randomly arranged on a page. Part A requires the connection of numbers in order, and part *B r*equires the sequencing of numbers and letters in alternating ascending order.

***Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Subtests*** *(Wechsler, 1997)*:

***Digit Span (3 min) –*** a measure of attention and sustaining concentration

***Digit Symbol (3 min) –*** a spatial measure involving learning and speed

***Similarities* (*10 min*)** – higher level verbal abstraction and reasoning, will also be used as an estimate of premorbid function

**Mood and Health Questionnaires**

***Environmental Worry Scale (EWS)*** (Bowler and Schwarzer, 1991)

This scale is a 17-item measure developed to predict intention to avoid chemicals and has satisfactory psychometric properties. A 5-item version was used in this study to examine participants' particular concerns about chemical exposures, which is also has satisfactory normative properties.

***Health-Related Quality of Life Scale (BRFSS)***(Centers for Disease Control and Prevention)

This scale is a brief 4-item scale developed by the Centers for Disease Control and Prevention to assess self-perceived recent health, recent mental health and activity limitations. Nationwide normative data is available.

***Satisfaction with Life Scale*** (Diener et al., 1985)

This 5-item scale is a brief measure of life satisfaction. It asks participants to compare the current status of their life to their self-defined expectations of how they would like their lives to be. It has satisfactory psychometric properties.

***Symptom Checklist-90-Revised (SCL-90-R)*** (Derogatis, 1992)

A 90-item standardized scale asking participants to rate how much of a problem certain symptoms had been in the prior week, using a five-point scale. Domains/scales are: Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, Psychoticism, and summary indices.

***General Health questionnaire:***

A health questionnaire will be administered in a printed format. It will include socio-demographic information, smoking and drinking habits, hobbies with exposure to neurotoxic substances (gardening using pesticides, solvents, painting, welding etc), a history of illnesses and familial illnesses (with emphasis on neurological disorders), accidents and current symptoms (sleep, respiratory, cardiovascular, musculo-skeletal, neurologic and neuropsychiatric).

**Tests of Effort**

***Victoria Symptom Validity Test (VSVT)*** *(Slick et al., 2005)*

This computerized test is used to assess effort on memory tests and memory complaints exaggeration. The VSVT includes the presentation of 48 five-digit numbers and the forced-choice delayed identification of that number. Protocols where the number of correct items is above chance (50%) are considered valid. (15 minutes).

***Rey's 15-Item Visual Memory Test*** (Strauss et al., 2006)

It consists of a card with 15 printed items (letters, numbers and shapes) arranged in 3 columns and 5 rows. The examinee is told there are 15 different (emphasized) items to remember which are to be reproduced immediately on a blank sheet of paper following a 10-second exposure to the stimulus card. Although it is presented as a difficult task, it is actually quite simple because there is redundancy among items that reduces the amount

of information to be remembered (i.e. three main ideas). It is used to test motivation and potential deficit exaggeration.

**Neurological examination**

The motor/movement components and activities of daily living of the Unified Parkinson's disease Rating Scale (UPDRS) will be administered. The UPDRS is the most widely used scale for evaluation of clinical impairment in motor function. It contains 27 items, including assessments of posture, gait, postural stability, bradykinesia, and general hand and leg movements and tremor. It has good reliability and validity, utilizing the standardized test methodology and videotaped reference guide developed by (Goetz et al., 2003). It includes the Activities of Daily Living section (UPDRS II) and has 13 items of speech and daily activities and tasks. All items are rated on a scale of 0 (normal) to 3 or 4, depending on the scale with clinical descriptor for each rating ranging from normal to severe.

**Movement, Motor and Tremor** *(In alphabetical order)*

**Computerized Adaptive Testing System** (Danish Product Development, 1996)

1) **CATSYS hand tremo**r test. Hand tremor will be measured using the TREMOR 7.0 Test System. Vibrations within each hand are recorded with the TREMOR PEN. A two-axis micro-accelerometer is embedded within the tip of the 12 cm x 0.8 cm TREMOR PEN, which is connected to a PC data log system. The TREMOR PEN is sensitive to vibrations that occur in a plane perpendicular to the PEN axis. Vibrations will be analyzed using the Fourier Power Spectrum, which plots the normalized power distribution (the relative harmonic contents) of the vibration measurement period in a frequency domain. The Harmonic Index, highly sensitive to abnormal tremor patterns, relates the Fourier Power Spectrum to that of a single harmonic oscillation.
2) **CATSYS postural sway** test. This test of postural stability will be performed in three conditions (35 seconds in each condition) while the participant stands on a 50 cm platform balance plate with a) eyes open , b) eyes closed, and c) eyes closed standing on 2 cm foam. Postural stability is measured in Mean Sway (mean of force center position to all recorded center positions), Transversal Sway (sway movement from side to side), and Sagittal Sway (sway movement back and forth). A Sway Index (in relation to normative age-adjusted data) is computed for each condition.

***Fingertapping Test*** (Lezak et al., 2004)

A measure of bilateral psychomotor speed; The participant is asked to tap a lever as quickly as possible. Scores are the mean of five 10-second trials for each hand.

***Grip Strength*** *(Dynamometer)* (Lezak et al., 2004)

A test of grip strength with two trials administered bilaterally.

***Grooved Pegboard Test***(Lezak et al., 2004)

Tactile speed and visuomotor coordination; Pegs are inserted in the slots as quickly as possible; pegs have a ridge on one side, requiring a rotation to line them up with the slots. Completion time is recorded for each hand.

***Parallel Lines - Graphomotor Tremo****r*(Lezak et al., 2004)

Graphomotor tremor will be assessed by drawing lines as straight as possible within defined 3-inch and 1-inch high boundaries without lifting the pencil from the paper. Qualitative evaluation of tremor by a neuropsychologist with ratings of within normal limits, mild, moderate, or severe.

## Appendix C. 2000 US Census Demographic Factors

| | | East Liverpool | % | Marietta | % | Mount Vernon | % |
|---|---|---|---|---|---|---|---|
| NO. TOTAL POPULATION | | 13,089 | | 14,515 | -- | 14,375 | -- |
| PLACE OF BIRTH | % US-BORN (UB) | -- | 99.1 | -- | 98.8 | -- | 98.4 |
| | % OH-BORN (OF UB) | -- | 74.2 | -- | 66.7 | -- | 81.5 |
| | % FOREIGN-BORN (FB) | -- | 0.5 | -- | 1.2 | -- | 1.6 |
| | % NON-CITIZEN (OF FB) | -- | | -- | 43.2 | -- | 40.7 |
| POVERTY | % BELOW POVERTY | -- | 12.4 | -- | 16.9 | -- | 15.6 |
| RACE | NO. WHITE | 12,153 | 92.8 | 13,979 | 96.3 | 13,895 | 96.7 |
| | NO. BLACK | 630 | 4.8 | 157 | 1.1 | 166 | 1.2 |
| | NO. OTHER | 306 | 2.3 | 379 | 2.6 | 314 | 2.1 |
| ETHNICITY | NO. HISPANIC | 94 | 0.7 | 114 | 0.8 | 125 | 0.9 |
| SEX | NO. MALE | 6,070 | 46.4 | 6,757 | 46.6 | 6656 | 46.3 |
| | NO. FEMALE | 7,019 | 53.6 | 7,758 | 53.4 | 7,719 | 53.7 |
| AGE | MEDIAN AGE, YEARS | 35.7 | | 38.4 | -- | 37.1 | -- |
| | MEDIAN AGE MALE | | | 36.1 | -- | 33.9 | -- |
| | MEDIAN AGE FEMALE | | | 40.4 | -- | 40.0 | -- |
| | NO. 65+ YEARS | 2,100 | 16 | 2,573 | 17.7 | | 18.3 |
| | NO. FEMALE 15-45 YEARS (% ♀) | | | 3,330 | 42.9 | 3,051 | 39.5 |
| | NO. PRE-SCHOOL ≤ 5 YEARS | | | 947 | 6.5 | 1,171 | 8.1 |
| | NO. SCHOOL AGE 6-18 YEARS | | | 2,400 | 16.5 | 2,429 | 16.9 |
| | NO. 7-8 YEARS | | | 351 | -- | 406 | -- |
| | NO. 9-10 YEARS | | | 325 | -- | 370 | -- |
| | NO. 35-65 YEARS | | | 5,412 | -- | 5,075 | -- |
| | NO. 25+ YEARS | | | 9,381 | 64.6 | 9,504 | 66.1 |
| EDUCATION (FOR 25+ YRS) | % LESS THAN HIGH SCHOOL | -- | 26.6 | -- | 15.9 | -- | 19.8 |
| | % HIGH SCHOOL | -- | 45 | -- | 34.9 | -- | 39.5 |
| | % SOME COLLEGE | -- | 21.2 | -- | 25.9 | -- | 22.6 |
| | % COLLEGE | -- | 2.7 | -- | 12.8 | -- | 10.9 |
| | % MORE THAN COLLEGE | -- | | -- | 10.4 | -- | 7.2 |
| NO. HOUSING UNITS (HU) | | 5,728 | -- | 6,609 | -- | 6,713 | -- |
| | NO. URBAN | | | 6,426 | 97.2 | 6,543 | 97.5 |
| | NO. RURAL | | | 183 | 2.8 | 170 | 2.5 |
| | % BUILT BEFORE 1970 | | | -- | 75.5 | -- | 75.0 |
| | MEDIAN YEAR BUILT | | | 1948 | -- | 1952 | -- |
| NO. HOUSEHOLDS (HH) | | | | 5,904 | -- | 6,187 | -- |
| | AVERAGE HH SIZE, PERSONS | 2.4 | -- | 2.2 | -- | 2.2 | -- |
| | MEDIAN HH INCOME | $23,138 | -- | $29,272 | -- | $29,801 | -- |

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Rosemarie Bowler, Ph.D.
8371 Kent Drive.
El Cerrito, CA 94530
Tel: 510/236-5599
Fax: 510/236-3370

August 1, 2011

RE: **East Liverpool Community Health Study**

**XXXX or current resident**
**Street Address**
**City, State Zip**

Dear XXXX or current resident,

My name is Professor Rosemarie Bowler, a faculty member at San Francisco State University in the Psychology Department. You may have seen in the local media that we are conducting research on the potential health effects of exposure to manganese in adults in your community. To examine these health effects, we are recruiting 100 adults in East Liverpool for participation. You have been randomly selected as a possible participant in our study. Any two members of your household between 30-75 years of age are invited to take part in study.

Each person participating in the study will receive a $50.00 gift card to Walmart as a token of our appreciation. Additionally, we will give you your personal results of the health screening. The total time commitment we ask of you may be up to 4 hours. Testing is taking place at the XXX Hotel on XXX St. in East Liverpool on October XX, XX, XX & XX mornings and afternoons. Participation in this study will involve asking you about your health and residential history, sleep, diet, and mood status. We also ask you to allow us to give you some tests to measure cognitive functioning, including memory, attention, learning, and visual/spatial skills. We will also be giving some tests of dexterity and strength. A movement neurologist will assess you briefly and a physician will review your medical history. Additionally, we will ask you for permission to draw a small blood sample, which will be analyzed in a certified laboratory for levels of manganese and other chemicals and that you provide a small sample of your hair and toenail clippings from each toe, which will be analyzed in a certified laboratory for levels of metals. All of your information will be kept confidential.

This research is being conducted with guidance from many partners, including the Ohio Department of Health, Mr. Michael Mullen, mayor of East Liverpool, the East Liverpool City Health District's health commissioner, Jelayne Dray, the Region 5 Environmental Protection Agency (EPA), and the Agency for Toxic Substances and Disease Registry.

If you are interested in participating in the study, please complete the enclosed stamped postcard with your name, phone number, and email if you use it, and mail it to us at your earliest convenience. Alternatively, you can send us an email with your name, address, and phone number at ohstudy@sfsu.edu. Once we receive this card from you we will contact you by phone and a representative of our study team will ask you a few questions to determine if your background meets the study participation criteria, e.g., not having a severe, advanced major illness. We will also answer any questions you might have about the study.
Thank you for considering participating in the East Liverpool Community Health Study!

Sincerely,

Rosemarie L. Bowler, Ph.D.

Rosemarie Bowler, Ph.D.

# East Liverpool Phone Recruitment Script

Hello, my name is _____. I am a _____ at San Francisco State University in the Psychology Department. We are conducting research on the potential health effects of exposure to manganese in adults. This study is supported by the United States Environmental Protection Agency, or USEPA, the Ohio Department of Health, the Ohio EPA, as well as the Columbiana County Health Department. You may have attended or heard about the town meeting where we discussed the study. I am calling because you live in proximity to some of the warehouses that may release manganese and other chemicals into the air and there is concern that this may have a negative health effects. Therefore, we would like you to consider allowing us to test your health. We are recruiting 100 adults in your town to participate in our study.

For this study we are only recruiting current residents of East Liverpool. Are you currently living in East Liverpool? **[IF YES]** And have you lived there for at least 10 years?

**[IF NO]** Unfortunately, we are only looking for residents who have been living in the community for at least 10 years, so we cannot ask you to participate. Thank you very much for you time, and have a great morning/afternoon/evening.

**[IF YES]** Great. Now I would like to describe to you some of the details of the study and also ask some questions to determine if you are eligible to participate in the study. Regardless of whether you are chosen for the study or not, this information will be kept strictly confidential. Only authorized researchers will have access to it, and it will be stored in a secure locked cabinet in the investigator's office. Even if you are ineligible to participate, your information will be kept in a locked file cabinet in the investigator's office and will be destroyed after 5 years. Would you like to continue?

Participation in this study will involve a brief interview about your health history, in addition to questionnaires regarding your medical, social, and psychological history. You would also be given tests to measure areas of cognitive functioning, including memory, attention, learning, and visual/spatial skills. We will also ask you to complete a brief neurological test of movement. Additionally, we will ask you for permission to collect a small sample of your hair, to collect your toenail clippings and draw a small amount of blood. The hair, toenails, and blood samples will be analyzed in a certified laboratory for manganese and other chemicals. The total time commitment would be approximately 2.5-4 hours.

If you're willing to participate and you are selected to be in our study, upon completion we will present you with a $50 gift card to Walmart as a token of our appreciation for your time. At a later time we will also notify you of your test results.

Would you be willing to answer some screening questions to determine your eligibility for our research study?

**[IF NO]** Thank you very much for your time and have a great morning/afternoon/evening.

**[IF YES]** Now I would like to ask the questions that I mentioned before. It should only take a few moments.

Sex: M F Age: _____ Years of Education: _____

Ethnicity: _____

1. Have you ever lived outside of East Liverpool, Ohio? Yes/No
2. Have you ever worked for S.H. Bell? Yes/No
3. Have you ever had any major exposure, which required a hospital visit, to
   Pesticides? Yes/No If yes, Name if you know?_____
   Fungicides? Yes/No If yes, Name if you know?_____
   Herbicides? Yes/No If yes, Name if you know?_____
   Carbon monoxide? Yes/No
   Heavy metals? Yes/No Name if you know?_____
4. Have you ever had a head injury or stroke? Yes/No
5. If so, did you require a hospital visit for more than 1 day? Yes/No
6. Have you ever been told by a doctor that you have:
   Parkinson's disease? Yes/No
   Huntington's disease? Yes/No
   Epilepsy? Yes/No
   Brain surgery? Yes/No
   Encephalitis? Yes/No
   Meningitis? Yes/No
   Multiple sclerosis? Yes/No
   Chronic liver disease? Yes/No
7. Have you ever undergone electroconvulsive treatment? Yes/No
8. Have you ever been told by a doctor that you have:
   Bipolar disorder? Yes/No
   Alzheimer's disease? Yes/No
   Schizophrenia or psychoses? Yes/No
9. Are you currently being treated for alcohol or drug dependence? Yes/No

If you would kindly give me your address, we can send you a written description of our study in the mail which will give you more information.

If you are selected to be in the study, we will be contacting you again by phone 6-8 weeks prior to the study in order to set up an appointment. If you would like to contact us in the meantime, we can be reached at 510-236-5599 or at this email address: ohstudy@sfsu.edu.
Thank you again for your interest, and have a great morning/afternoon/evening

## Telephone Appointment Reminder Script—East Liverpool

Hello Mr./Ms. XXXX,
My name is _____. I am calling to remind you about your appointment to participate in our research study on the potential health effects of exposure to manganese in adults. Your appointment is at XX am/pm on Day/Month/Year. The appointment will last an average of 2.5 to 4.0 hours. We hope to see you at that time. The address of the location is XXXXXXXX.

Please make sure to bring your glasses, if you wear any, and a list of all medications you are currently taking.

If you have any questions, need directions, or need to cancel the appointment, you can contact us at (510) 236-5599

Thank you for your time.

**San Francisco State University**

**Informed consent to participate in the following research study:**

**Relationship of airborne manganese exposure to neurobehavioral and health status of adults**

## A. PURPOSE AND BACKGROUND

The researcher of this study, Rosemarie Bowler, Ph.D., is a professor emerita of Psychology at San Francisco State University. The purpose of this study is to determine if there are negative health effects from exposure to airborne manganese and other chemicals in adults. You are being invited to participate in this study because you are a long term resident (10 or more years) of East Liverpool, Ohio and between the ages of 35 and 75. Your participation in this study is completely voluntary.

## B. PROCEDURES

If you agree to participate, the following will occur:

- All procedures will take place in our field office in East Liverpool.
- You will be interviewed about your health history. The interview will last approximately 15 minutes.
- You will be asked to complete questionnaires on your medical, social, and psychological history. This will take you about 60 minutes.
- You will be given tests used to measure multiple areas of cognitive functioning, such as general intellectual ability, memory, attention, learning, language, and visual and spatial skills. These tests will take no more than 75 minutes.
- Your motor functioning will be examined with tests of hand strength, balance and tremor, and dexterity. These will take approximately 15 minutes to complete.
- 12 mL (about 2 teaspoons) of blood will be drawn from a vein in your arm by a certified phlebotomist (a person trained to collect blood samples). Your blood will be securely shipped to, stored, and analyzed at the Centers for Disease Control and Prevention (CDC) Environmental Health Laboratory under the direction of the assistant chief of the laboratory, Kathleen Caldwell, Ph.D. Your blood will be analyzed for the following compounds: manganese, lead, mercury, and cadmium, in addition to iron and 2 liver enzymes.
- We will ask you to provide small amounts of your hair (a small sample taken from the back of the head underneath other hair so it will not be noticeable) as well as toenail clippings from all 10 toes. These samples will be analyzed in order to evaluate your exposure to metals.
- Your toenail and hair clippings will be securely shipped to, stored, and analyzed at the Harvard School of Public Health Trace Metals Laboratory. Your toenail clippings will be analyzed for levels of metals.
- Your participation in this study will take an average of 2.5 to 4.0 hours.

## C. RISKS

**1)** When blood is drawn, there is a risk of experiencing slight pain or a prick where the needle punctures the skin. There is also a slight risk of bruising or an infection where the needle punctures the skin. In rare cases, some people may experience lightheadedness, nausea, or fainting. The certified phlebotomist is trained in recognizing and dealing with such reactions. A licensed medical doctor (M.D.) will be on call nearby at all times and will give a consultation in case of a medical emergency for appropriate emergency medical care.

**2)** Participation in research may involve some possibility of loss of privacy. This risk will be reduced to the extent possible. More information about this risk and how we will reduce it appears in the confidentiality section below.

**3)** You may feel slight fatigue during testing. Should this occur, you can choose to take a break or discontinue testing at any point.

**4)** Some of the questions in the questionnaires may be personal and sensitive in nature. You are not required to answer a particular question if you feel uncomfortable.

**5)** It is possible that results from the blood analysis could reveal serious health problems that you are not aware of. After the analysis, you will be given a report indicating all your test results, and if anything serious is found, you are advised to consult with your family doctor or a local healthcare provider.

**6)** There may be risks and discomforts that are not yet known.

**7)** The researchers, research team and sponsors of this project will not provide medical care to participants nor will they cover the cost of medical care for participants.

## D. CONFIDENTIALITY

Your information will be handled confidentially. Your name will not be used in any published reports about this study. Your results will be entered into a computer database without your name or other identifiers. An ID number will be assigned to all of your test results and only Professor Rosemarie Bowler will be aware of your identity and ID number. The data will be handled only by research staff, all of whom will sign a special confidentiality contract, and will be entered in a password-protected computer database. All research records and test results will be stored in locked file cabinets. All electronic data and results will be kept in an encrypted document on a password-protected computer. Your information will not be released unless subpoenaed by a court of law. All biological samples will be stored in secure laboratory facilities. We would like to store any blood that is left over after we finish your lab tests in a facility which will provide secure storage. We may use the specimens in future studies. We will link the study data with the blood samples using only your ID number, but will not report back these future analyses. Even if you decide not to let us store your blood for future use, you can still be in this current study. All data will be maintained for approximately 5 years in hard copy with access limited to only authorized individuals. The electronic data will be securely stored indefinitely. Unauthorized access will be reported to the relevant parties (participants, stakeholders). Electronic data will be saved on a device that has the appropriate security safeguards (password protection, etc).

## E. DIRECT BENEFITS

You will receive the test results in writing, which you can send to your physician. We will indicate whether any results are of concern. If abnormalities are found, you will be referred to your family physician.

## F. COSTS

There is no cost to you for participating in this research, aside from the transportation costs of coming to the appointment. Transportation costs involved in come to the field office will not be reimbursed. Medical care will not be provided by the researchers or research team nor will medical care costs be covered.

## G. COMPENSATION

You will be presented with a $50 Wal-Mart gift card, as a token of appreciation for your participation in the study. Early withdrawal from the study or incompletion of a major parts of the study will not be compensated monetarily.

## H. ALTERNATIVES

The alternative is not to participate in the research.

## I. QUESTIONS

You have spoken with Professor Rosemarie Bowler or one of her collaborators about this study and have had your questions answered. If you have any further questions about the study, you may contact the researcher by email at rbowl@sfsu.edu or by phone at 510-236-5599. Questions about your rights as a study participant, or comments or complaints about the study also may be addressed to the Office for the Protection of Human Subjects at San Francisco State University, at 415-338-1093 or protocol@sfsu.edu.

## J. CONSENT

**You have been given a copy of this consent form to keep.**

**PARTICIPATION IN THIS RESEARCH STUDY IS VOLUNTARY. You are free to decline to participate in this research study. You may withdraw from this study at any point without penalty. Even if you sign, you may stop at any time. Your decision to take part in this research will have no influence on your present or future status at San Francisco State University.**

Name _____

Signature _____ Date _____
Participant

Signature _____ Date _____
Researcher

I consent to the storage and future use and analyses of my blood. _____ Initial

## AUTHORIZATION
## TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

**Why is this authorization required?**
The US Government has issued a new rule, called the Privacy Rule, effective April 14, 2003. This rule requires Rosemarie Bowler Ph.D. and her colleagues to safeguard your Protected Health Information. Protected Health Information also includes information about you that could be used to link your identity to your health information. It also includes the information in your medical record. Your medical and health information will remain private as far as any identification of your name and will be used in the research database using only your ID number. However, to further protect your personal health information and to satisfy governmental rules, you are asked to also sign this Health Insurance Portability and Accountability Act (HIPAA) Consent, which will also be stored separate from the research data files.

The purpose of this section is to explain to you how Rosemarie Bowler Ph.D. and her research colleagues propose to use and disclose your health information for the purpose of this study. None of your health information gained in this current research study will be used or disclosed without your written permission.

**Must you agree to this authorization to participate in the research?**
To participate in this research study, you must agree to authorize the use and disclosure of your health information as described above. If you do not approve this use, you cannot participate in this study.

**Why will your health information be used or disclosed for this study?**
Rosemarie Bowler Ph.D. and research colleagues who are part of the team, consisting of neurologists, a toxicologist, neuropsychologists and experts on exposure, will use your health information to conduct the study, monitor your health status, and determine research results. Your health information will be used in the research study to identify if certain illnesses occur more often with certain levels of Mn air emissions and levels of Mn in blood. Your health information will not be disclosed outside Professor Bowler's research as part of this study, unless required by law. You will receive a letter notifying you of any abnormal results of the study if this will be determined by a qualified doctor who will review your results and will be working with the research team.

**Who will use your information, and what is the purpose of this use?**
If you sign this authorization, Professor Bowler and her research team may use your health information. They will use your study research record and information from your neuropsychological/medical record which included laboratory tests, and research observations made during your participation in the study.

Professor Bowler and research team may also disclose your health information to research colleagues other than the investigators, who may be asked to rate your results without any identifiers. These persons will be bound under the same confidentiality rules as the investigators of the study.

**When will this authorization expire?**
This authorization will expire at the end of this research study.

**Can you withdraw the authorization?**
At any time during this study, you may decide that you no longer want to have your information used or disclosed as part of this study. If so, you must write a letter stating that you withdraw your authorization and send it to: Rosemarie Bowler Ph.D., 8371 Kent Drive, El Cerrito, CA 94530.

If you withdraw your authorization, you may be required to end your participation in the study.

If required by research procedures, Rosemarie Bowler Ph.D. and the other researchers may continue to use health information that was obtained before you withdrew your authorization unless you specifically request to have your data removed.

Even if you withdraw your authorization, Rosemarie Bowler Ph.D. and her colleagues are required by law to record and report anything that relates to the safety of others.

**What will happen to my information after it is disclosed?**
Professor Bowler's research team will use and disclose your health information only as permitted by you in this authorization. However, collaborating investigators will have signed a confidentiality agreement.

**Will you get a copy of authorization?**
The researcher who is obtaining this authorization form must give you a copy of this form after you sign it.

**Authorization signatures**
Your signature indicates that this authorization has been explained to you, all of your questions have been answered, and you agree to allow the use and disclosure of your health information for the research as described below.

_____ _____
Signature of Participant Date

_____
Name of Participant

Rosemarie Bowler, Ph.D.
8371 Kent Drive
El Cerrito, CA 94530
Tel: 510/236-5599
Fax: 510/236-3370

SAMPLE East Liverpool Feedback Letter

Dear XXXXX,

Thank you again for participating in the East Liverpool Community Health Study investigating the possible health effects of manganese exposure in adults. Enclosed you will find your personal results of the neurological and neuropsychological testing, as well as the results of your blood analysis. Thank you for providing your information to us. If you have questions about your individual results, please email your questions to:ohstudy@sfsu.edu or you can contact me at 510-236-5599.

We very much appreciate your participation in this community study of airborne manganese exposure in adults. It has been a privilege to have your cooperation in our study and we encourage you to contact us if you have additional questions or concerns you would like to discuss.

Sincerely,

Rosemarie Bowler, Ph.D., M.P.H.

**Dear «First_Name_1» «Last_Name_1»**
The tables below show the behavioral and laboratory test results from your participation in the 2011 East Liverpool Community Health study investigation of effects of air manganese exposure on adults in the community of East Liverpool, Ohio.

## Neuropsychological & Neurological Test Results:

| Area of function: | Description: | Results: |
|---|---|---|
| Motor Speed | Speed of performance of both hands | Wnl (within normal range) |
| Other Motor | Strength, manual dexterity, and tremor | Outside of normal range |
| Movement | Body stability, muscle tone, reflexes | Wnl (within normal range) |
| Attention | Attention, concentration, short-term memory | Wnl (within normal range) |
| Visual Memory | Long-term visual memory | Wnl (within normal range) |
| Auditory Memory | Long-term auditory memory | Outside of normal range |
| Cognitive Flexibility | Ability to perform complicated tasks | Wnl (within normal range) |
| Mood | Emotional functioning | Wnl (within normal range) |

If any of your test results are different from those found in the general population (outside of the normal range), you are advised to consult with your family doctor or a local healthcare provider. Please note that any medical care will be at your own expense. Note: Test results outside of the normal range may not result in a diagnosis.

Rosemarie Bowler, Ph.D.
8371 Kent Drive
El Cerrito, CA 94530
Tel: 510/236-5599
Fax: 510/236-3370

## Blood Analyses Results:

| Lab test | Your Value | Found in General Population |
|---|---|---|
| Manganese (Mn) [1] | X µg/L | 4.0 to 15 µg/L |
| Lead (Pb) [2] | X µg/dL | 1.40 to 4.20 µg/dL |
| Cadmium (Cd) [2] | X µg/L | 0.3 to 1.3 µg/L |
| Mercury (Hg) [2] | X µg/L | 0.3 to 1.9 µg/L |
| Ferritin (Ferr-S) [3] | X ng/mL | Female: 10 – 120 ng/mL<br>Male: 20 – 250 ng/mL |

[1] http://www.atsdr.cdc.gov/toxprofiles/tp151.html – Chapter 1, p 8
[2] Based on National Health and Nutrition Survey years 2003-2004, U.S. general population upper 50th and 95th percentile.
Note: The measurement of an environmental chemical in a person's blood does not by itself mean that the chemical causes disease

## Toenail Analyses Results:

| Lab test | Your Value | Found in General Population |
|---|---|---|
| Manganese (Mn) | XXX | XX to XX |

## Hair Analyses Results:

| Lab test | Your Value | Found in General Population |
|---|---|---|
| Manganese (Mn) | XXX | XX to XX |

SAN FRANCISCO STATE UNIVERSITY

# East Liverpool Health Study

**Are you a 30-75 year old resident who has lived in East Liverpool for at least 10 years?**

***Please fill out the back of this card and mail it if you, or another member of your household, are interested in participating in the study.***


**Rosemarie Bowler, Ph.D.**
**Health Study Office**
**8371 Kent Drive**
**El Cerrito, CA 94530**



SAN FRANCISCO STATE UNIVERSITY

East Liverpool Health Study

Are you a 30-75 year old resident who has lived in East Liverpool for at least 10 years?

*Please fill out the back of this card and mail it if you, or another member of your household, are interested in participating in the study.*



Rosemarie Bowler, Ph.D.
Health Study Office
8371 Kent Drive
El Cerrito, CA 94530

# Study Response Card

Your reply is kindly requested ASAP or before XXXXXXXX.
Two people from a household can participate.
Thank you!

Please check if interested

☐ I am interested in participating in the East Liverpool health study and I give my permission for the researchers to contact me using the information below.

1. _____ _____
First Name Last Name

2. _____ _____
First Name Last Name

_____ _____ _____
Street Address City Zip code

( _ _ ) _ _ - _ _ _ _ _ _ _ _ _ _ _ _ @ _ _ _ _ _ _ _ _ _ _ _ _
Telephone Number Email address


# Study Response Card

Your reply is kindly requested ASAP or before XXXXXXXX.
Two people from a household can participate.
Thank you!

Please check if interested

☐ I am interested in participating in the East Liverpool health study and I give my permission for the researchers to contact me using the information below.

1. _____ _____
First Name Last Name

2. _____ _____
First Name Last Name

_____ _____ _____
Street Address City Zip code

( _ _ ) _ _ - _ _ _ _ _ _ _ _ _ _ _ _ @ _ _ _ _ _ _ _ _ _ _ _ _
Telephone Number Email address

ID_____

# Environmental Worry Scale

| Please √ only one | Not at all true | Barely true | Moderately true | Exactly true |
|---|---|---|---|---|
| **1.** I don´t worry about being hurt by chemicals | ❑ | ❑ | ❑ | ❑ |
| **2.** I feel worried about toxic effects on my body which might result in losing some of my intellectual abilities. | ❑ | ❑ | ❑ | ❑ |
| **3.** Many people tend to overreact to the threat of environmental toxins. | ❑ | ❑ | ❑ | ❑ |
| **4.** Poor memory can be a direct result of too much exposure to chemicals | ❑ | ❑ | ❑ | ❑ |
| **5.** Being exposed to most chemicals for a long time does not cause serious diseases. | ❑ | ❑ | ❑ | ❑ |

36139

Name: _____

(For office use.)

## Satisfaction with Life Scale

Below are five statements that you may agree or disagree with. Using the 1-7 scale to the right, indicate your agreement by filling in the appropriate bubble next to each item. Please be open and honest in your responding.

**Scale:**
**1 = Strongly disagree**
**2 = Disagree**
**3 = Slightly disagree**
**4 = Neither agree nor disagree**
**5 = Slightly agree**
**6 = Agree**
**7 = Strongly agree**

| | Strongly disagree | Disagree | Slightly disagree | Neither agree nor disagree | Slightly agree | Agree | Strongly agree | |
|---|---|---|---|---|---|---|---|---|
| 1 | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | In most ways my life is close to my ideal. |
| 2 | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | The conditions of my life are excellent. |
| 3 | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | I am satisfied with my life. |
| 4 | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | So far I have gotten the important things I want in life. |
| 5 | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | If I could live my life over, I would change almost nothing. |

## Quality of Life Scale

**1** Would you say that in general your health is: (Fill in appropriate bubble.)

◯ **Excellent** ◯ **Very good** ◯ **Good** ◯ **Fair** ◯ **Poor**

**For items 2-4 below, please write in one number in each box, e.g., 3 days =** **0 3**

**2** Regarding your physical health, which includes physical illness and injury, for how many days during the past 30 days was your physical health not good? ☐☐ **0-30 days**

**3** Regarding your mental health, which includes stress, depression, and problems with emotions, for how many days during the past 30 days was your mental health not good? ☐☐ **0-30 days**

**4** During the past 30 days, for about how many days did poor physical or mental health keep you from doing your usual activities, such as self-care, work, or recreation? ☐☐ **0-30 days**

ID:_____

# Health Study Questionnaire

Please complete the attached questionnaire.

Your answers will be kept confidential.

Ask a staff person if you are not sure about any of the questions.

You can skip any questions you prefer not to answer.

You may be interrupted if a tester needs you for another test, but can continue to answer the questionnaire items after this interruption.

**Thank you for completing the questionnaire.**

ID:_____

# Health Study Questionnaire

## SECTION I: RESIDENCE INFORMATION

**1.** How many years have you lived in East Liverpool? _____ **years**

**2.** Address: **(Please list the addresses of the last 3 places you have lived for more than a year)**

**A. Current Address:**
Street address _____ From: month _____ year _____
City _____ State ___ ZIP _____ To: Present

**B. Previous (most recent) address:**
Street address _____ From: month _____ year _____
City _____ State ___ ZIP _____ To: month _____ year _____

**C. Previous address:**
Street address _____ From: month _____ year _____
City _____ State ___ ZIP _____ To: month _____ year _____

**D. If you have lived at more than 3 addresses for more than 1 year, please let us know and we will provide you with a supplemental residency sheet.**

**3.** Are you on the public water supply?
- ❑ Yes
- ❑ No

## SECTION II: SYMPTOMS

**Are you experiencing any of the following symptoms?**
(**Please** √ and, IF YES, write in **year** started.)

ID:_____

| | NO | YES | When did you experience it for the first time? (year) | How many times did you experience this in the LAST MONTH? |
|---|---|---|---|---|
| 1. Problems sleeping | ❑ | ❑ | | |
| 2. Problems falling asleep | ❑ | ❑ | | |
| 3. Waking up too often | ❑ | ❑ | | |
| 4. Waking up too early | ❑ | ❑ | | |
| 5. Having nightmares | ❑ | ❑ | | |
| 6. Night sweats | ❑ | ❑ | | |
| 7. Difficulty waking up in the morning | ❑ | ❑ | | |
| 8. Difficulty staying awake during the day | ❑ | ❑ | | |
| 9. Awakening with muscle cramps | ❑ | ❑ | | |
| 10. Blurred vision | ❑ | ❑ | | |
| 11. Changes in handwriting | ❑ | ❑ | | |
| 12. Changes in sense of smell | ❑ | ❑ | | |
| 13. Changes in sense of taste | ❑ | ❑ | | |
| 14. Changes in walking | ❑ | ❑ | | |
| 15. Confusion or feeling lost | ❑ | ❑ | | |
| 16. Cough | ❑ | ❑ | | |
| 17. Cramping in legs | ❑ | ❑ | | |
| 18. Dark vision | ❑ | ❑ | | |
| 19. Diarrhea | ❑ | ❑ | | |
| 20. Dim vision | ❑ | ❑ | | |
| 21. Difficulty chewing | ❑ | ❑ | | |
| 22. Difficulty concentrating | ❑ | ❑ | | |
| 23. Difficulty driving because of feeling dizzy | ❑ | ❑ | | |
| 24. Difficulty getting out of chairs | ❑ | ❑ | | |
| 25. Difficulty sitting up straight | ❑ | ❑ | | |
| 26. Difficulty turning in bed | ❑ | ❑ | | |
| 27. Difficulty with skilled movements | ❑ | ❑ | | |
| 28. Difficulty writing | ❑ | ❑ | | |
| 29. Excessive perspiration | ❑ | ❑ | | |

**Are you experiencing any of the following symptoms?**
(**Please** √ and, IF YES, write in **year** started.)

| | NO | YES | When did you experience it for the first time? (year) | How many times did you experience this in the LAST MONTH? |
|---|---|---|---|---|
| 30. Excessive salivation | ❑ | ❑ | | |
| 31. Facial expression changes | ❑ | ❑ | | |
| 32. Facial muscle tightness | ❑ | ❑ | | |
| 33. Feeling anxious | ❑ | ❑ | | |
| 34. Feeling depressed | ❑ | ❑ | | |
| 35. Feeling irritable | ❑ | ❑ | | |
| 36. Feeling lightheaded or dizzy | ❑ | ❑ | | |
| 37. Fever, chills | ❑ | ❑ | | |
| 38. Hand or foot tapping | ❑ | ❑ | | |
| 39. Headaches at least twice a week | ❑ | ❑ | | |
| 40. Joint pain or swelling | ❑ | ❑ | | |
| 41. Loss of consciousness (fainting) | ❑ | ❑ | | |
| 42. Loss of coordination or balance | ❑ | ❑ | | |
| 43. Loss of muscle strength in arms/hand | ❑ | ❑ | | |
| 44. Loss of muscle strength in legs/feet | ❑ | ❑ | | |
| 45. Loss of sense of smell | ❑ | ❑ | | |
| 46. Lower tolerance for alcohol | ❑ | ❑ | | |
| 47. Metallic taste in mouth | ❑ | ❑ | | |
| 48. Migraine headaches | ❑ | ❑ | | |
| 49. Monotonous voice | ❑ | ❑ | | |
| 50. Muscle aches | ❑ | ❑ | | |
| 51. Muscle twitching | ❑ | ❑ | | |
| 52. Muscular rigidity | ❑ | ❑ | | |
| 53. Nausea not cause by something you ate | ❑ | ❑ | | |
| 54. Noticeable change in personality | ❑ | ❑ | | |
| 55. Numbness/tingling in fingers or feet, for more than one day | ❑ | ❑ | | |
| 56. Sexual dysfunction | ❑ | ❑ | | |
| 57. Shortness of breath on exertion | ❑ | ❑ | | |
| 58. Skin rash | ❑ | ❑ | | |

**Are you experiencing any of the following symptoms?**
(**Please** √ and, IF YES, write in **year** started.)

| | NO | YES | When did you experience it for the first time? (year) | How many times did you experience this in the LAST MONTH? |
|---|---|---|---|---|
| 59. Slowness of movement | ❑ | ❑ | | |
| 60. Slurred speech | ❑ | ❑ | | |
| 61. Stomach cramps / stomach pain | ❑ | ❑ | | |
| 62. Tremors or Shakiness (temporary) | ❑ | ❑ | | |
| 63. Tremors or Shakiness (long term) | ❑ | ❑ | | |
| 64. Trouble remembering things | ❑ | ❑ | | |
| 65. Urinary or Bowel incontinence | ❑ | ❑ | | |
| 66. Vomiting | ❑ | ❑ | | |
| 67. Wheezing or whistling in chest | ❑ | ❑ | | |
| 68. Weight fluctuation | ❑ | ❑ | | |
| 69. Respiratory problems on **'bad air'** days | ❑ | ❑ | | |
| 70. Bringing phlegm from chest into throat | ❑ | ❑ | | |
| 71. Dizziness <u>when in the presence of **gas**</u> | ❑ | ❑ | | |
| 72. Headaches <u>when in the presence of **gas**</u> | ❑ | ❑ | | |
| 73. Dizziness <u>when in the presence of **paint**</u> | ❑ | ❑ | | |
| 74. Headaches <u>when in the presence of **paint**</u> | ❑ | ❑ | | |

**75.** When you are driving and have just passed a light, do you worry that it was red? (please √ one)

❑ Never **(skip to 76 below)** ❑ Occasionally
❑ Rarely ❑ Frequently

**A.** When did you experience it for the first time? **(year)** _____

**B. How** many times did you experience this in the LAST MONTH? _____ **times**

**76.** Do you consider yourself allergic or unusually sensitive to everyday chemicals like those in household cleaning supplies, paints, perfumes, soaps, garden sprays or things like that?

❑ Yes
❑ No **(IF NO, skip to MEDICAL HISTORY section)**
❑ Not Sure/Don't' Know **(IF NOT SURE, skip to MEDICAL HISTORY section)**

**77. If YES,** how old were you when you first noticed this sensitivity? **_____ (age)**

**IF** you don't remember, did you have it:

- ❑ Entire life
- ❑ Don't remember what age, but not entire life
- ❑ Don’t know/ Not sure

**78.** Was there something that happened when you were that age that first triggered this sensitivity?

- ❑ Yes
- ❑ No **(IF NO, skip to MEDICAL HISTORY section)**
- ❑ Not Sure/Don’t’ Know **(IF NOT SURE, skip to MEDICAL HISTORY section)**

**79. IF YES, what was it?** _____

## SECTION III: MEDICAL HISTORY

**Have you ever been diagnosed <u>by a doctor</u> as having any of the following illnesses or conditions?**
(**Please** √ and, **IF YES**, write in the **year** when diagnosed.)

| | | | | Had it within the last year? | | |
|---|---|---|---|---|---|---|
| | **NO** | **YES** | **Year diagnosed** | **No** | **YES** | |
| 1. Acute Bronchitis | ❑ | ❑ | _____ | ❑ | ❑ | **How many times in last year?** _____ |
| 2. Pleurisy | ❑ | ❑ | _____ | ❑ | ❑ | |
| 3. Tuberculosis | ❑ | ❑ | _____ | ❑ | ❑ | |
| 4. Chest Injury | ❑ | ❑ | | ❑ | ❑ | |
| 5. Pneumonia | ❑ | ❑ | _____ | ❑ | ❑ | **How many times in last year?** _____ |
| 6. Chronic Bronchitis | ❑ | ❑ | | ❑ | ❑ | **How many times in last year?** _____ |
| 7. Emphysema | ❑ | ❑ | _____ | ❑ | ❑ | |
| 8. Asthma | ❑ | ❑ | _____ | ❑ | ❑ | **How many times in last year?** _____ |
| 9. Hay fever | ❑ | ❑ | _____ | ❑ | ❑ | |

**Have you ever been diagnosed <u>by a doctor</u> as having any of the following illnesses or conditions?**
(**Please** √ and, **IF YES**, write in the **year** when diagnosed.)

| | NO | YES | Year diagnosed | Had it within the last year? No | Had it within the last year? YES | |
|---|---|---|---|---|---|---|
| 10. High blood pressure | ❑ | ❑ | _____ | ❑ | ❑ | |
| 11. Heart trouble | ❑ | ❑ | _____ | ❑ | ❑ | |
| 12. Heart attack | ❑ | ❑ | _____ | ❑ | ❑ | **How many times in last year?** _____ |
| 13. Chest pain with exertion | ❑ | ❑ | _____ | ❑ | ❑ | |
| 14. Heart valve disease | ❑ | ❑ | _____ | ❑ | ❑ | |
| 15. Bone or joint cancer | ❑ | ❑ | _____ | ❑ | ❑ | |
| 16. Brain cancer | ❑ | ❑ | _____ | ❑ | ❑ | |
| 17. Breast cancer | ❑ | ❑ | _____ | ❑ | ❑ | |
| 18. Cancer of esophagus (swallowing tube), stomach, intestines, colon, rectum, liver, pancreas, or other digestive organs | ❑ | ❑ | _____ | ❑ | ❑ | |
| **IF YES,** which type?_____ | | | | | | |
| 19. Kidney or bladder cancer | ❑ | ❑ | _____ | ❑ | ❑ | |
| 20. Leukemia | ❑ | ❑ | _____ | ❑ | ❑ | |
| 21. Lymphoma or lymph system cancer | ❑ | ❑ | _____ | ❑ | ❑ | |
| 22. Lung or chest cancer | ❑ | ❑ | _____ | ❑ | ❑ | |
| 23. Multiple myeloma | ❑ | ❑ | _____ | ❑ | ❑ | |
| 24. Male or female organ cancer | ❑ | ❑ | _____ | ❑ | ❑ | |
| **IF YES,** which type?_____ | | | | | | |
| 25. Mouth or throat cancer | ❑ | ❑ | _____ | ❑ | ❑ | |

**Have you ever been diagnosed <u>by a doctor</u> as having any of the following illnesses or conditions?**
(**Please** √ and, **IF YES**, write in the **year** when diagnosed.)

| | NO | YES | Year diagnosed | Had it within the last year? No | YES | |
|---|---|---|---|---|---|---|
| 26. Nasal cancer | ❑ | ❑ | _____ | ❑ | ❑ | |
| 27. Skin cancer | ❑ | ❑ | _____ | ❑ | ❑ | |
| 28. Thyroid cancer | ❑ | ❑ | _____ | ❑ | ❑ | |
| 29. Cataracts | ❑ | ❑ | _____ | ❑ | ❑ | |
| 30. Glaucoma | ❑ | ❑ | _____ | ❑ | ❑ | |
| 31. Other eye problems (not related to glasses or contacts) | ❑ | ❑ | _____ | ❑ | ❑ | |
| **IF YES,** which type?_____ | | | | | | |
| 32. Anemia | ❑ | ❑ | _____ | ❑ | ❑ | **How many times in last year?** _____ |
| 33. Psychiatric / nervous disorder | ❑ | ❑ | _____ | ❑ | ❑ | |
| **IF YES,** which type?_____ | | | | | | |
| Were you given medication? | ❑ | ❑ | _____ | | | |
| **IF YES,** which medication?_____ | | | | | | |
| 34. Seizure disorder | ❑ | ❑ | _____ | ❑ | ❑ | |
| 35. Diabetes | ❑ | ❑ | _____ | ❑ | ❑ | |
| 36. Hepatitis, jaundice or other liver disease | ❑ | ❑ | _____ | ❑ | ❑ | |
| 37. Allergies | ❑ | ❑ | _____ | ❑ | ❑ | |
| **IF YES,** which type?_____ | | | | | | |
| 38. Skin rashes | ❑ | ❑ | _____ | ❑ | ❑ | **How many times in last year?** _____ |
| 39. Diseases of bones, joints, muscles | ❑ | ❑ | _____ | ❑ | ❑ | |

**Have you ever been diagnosed <u>by a doctor</u> as having any of the following illnesses or conditions?**
(**Please** √ and, **IF YES**, write in the **year** when diagnosed.)

| | NO | YES | Year diagnosed | Had it within the last year? No | Had it within the last year? YES | |
|---|---|---|---|---|---|---|
| 40. Kidney problems / infection | ❑ | ❑ | _____ | ❑ | ❑ | |
| 41. Bladder infection | ❑ | ❑ | _____ | ❑ | ❑ | **How many times in last year? _____** |
| 42. Cold sores or mouth ulcers | ❑ | ❑ | _____ | ❑ | ❑ | **How many times in last year? _____** |
| 43. Blood in urine | ❑ | ❑ | _____ | ❑ | ❑ | |
| 44. Thyroid disease | ❑ | ❑ | _____ | ❑ | ❑ | |
| 45. Head injury | ❑ | ❑ | _____ | ❑ | ❑ | |
| 46. Asbestosis | ❑ | ❑ | _____ | ❑ | ❑ | |
| 47. Rheumatic fever | ❑ | ❑ | _____ | ❑ | ❑ | |
| 48. Fainting spells | ❑ | ❑ | _____ | ❑ | ❑ | **How many times in last year? _____** |
| 49. Sinus trouble / Sinusitis | ❑ | ❑ | _____ | ❑ | ❑ | **How many times in last year? _____** |
| 50. Back or spine problems | ❑ | ❑ | _____ | ❑ | ❑ | |
| 51. Swollen lymph nodes | ❑ | ❑ | _____ | ❑ | ❑ | **How many times in last year? _____** |
| 52. Aplastic anemia | ❑ | ❑ | _____ | ❑ | ❑ | |
| 53. Niemann-Pick's disease | ❑ | ❑ | _____ | ❑ | ❑ | |
| 54. Alzheimer's disease | ❑ | ❑ | _____ | ❑ | ❑ | |
| 55. Amyotrophic Lateral Sclerosis (ALS), aka Lou Gehrig's disease | ❑ | ❑ | | ❑ | ❑ | |
| 56. Huntington's chorea | ❑ | ❑ | _____ | ❑ | ❑ | |
| 57. Multiple Sclerosis | ❑ | ❑ | _____ | ❑ | ❑ | |
| 58. Parkinson's disease | ❑ | ❑ | _____ | ❑ | ❑ | |

**Have you ever been diagnosed <u>by a doctor</u> as having any of the following illnesses or conditions?**
(**Please** √ and, **IF YES**, write in the **year** when diagnosed.)

| | NO | YES | Year diagnosed | Had it within the last year? No | YES |
|---|---|---|---|---|---|
| 59. Autoimmune Connective Tissue Disorders (Lupus, Rheumatoid arthritis) | ❑ | ❑ | _____ | ❑ | ❑ |
| 60. Tremor disorder | ❑ | ❑ | _____ | ❑ | ❑ |
| 61. Silicosis, aka Grinder's disease or Potter's rot | ❑ | ❑ | _____ | ❑ | ❑ |
| 62. Other major illness | ❑ | ❑ | _____ | ❑ | ❑ |

**IF YES,** which type?_____

63. Have you been hospitalized in the last 5 years? **No** ❑ **Yes**❑ **IF YES** what year?_____

**IF YES**, what was the condition? _____

If you were hospitalized more than once in 5 years, please list these below:

## SECTION IV: MEDICATIONS

1. Have you taken any medication in the last 24 hours (including prescription and over-the-counter)?

❑ Yes
❑ No **(IF NO, skip to question 4)**

2. What medication(s) did you take in the last 24 hrs.?_____

3. When did you first take that medication? _____**/**_____ **(month/year)**

4. Have you taken the following **over-the-counter** medications? If YES, please write the name/brand.

ID:_____

| Over-the-counter | NO | YES | If YES, please write name/brand | √ if taken in last month | If YES, how many do/did you take? Per Year | Per Month | Per Day |
|---|---|---|---|---|---|---|---|
| **1.** Antacids or Stomach Medicine (Maalox, Mylanta, Tums, etc.) | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **2.** Cough Medicine | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **3.** Cold Medications | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **4.** Skin Medications or Creams | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **5.** Headache Medicines | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **6.** Sleeping Pills | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **7.** Pain Medications (Aspirin, Tylenol, Advil, etc.) | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **8.** Iron Supplements | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **9.** Vitamin Supplements with Iron | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **10.** Herbal Medicine | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **11.** Other: | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |

5. Have you taken the following **prescription** medications? If YES, please write the name/brand.

| Prescription | NO | YES | If YES, please write name/brand | √ if taken in last month | If YES, how many do/did you take? Per Year | Per Month | Per Day |
|---|---|---|---|---|---|---|---|
| **1.** Prescribed Antacids or Stomach Medicine | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **2.** Antibiotics | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **3.** Arthritis Medicine | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **4.** Blood Pressure Medicine | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **5.** Medications for Asthma | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |

| Prescription | NO | YES | If YES, please write name/brand | √ if taken in last month | If YES, how many do/did you take? Per Year | Per Month | Per Day |
|---|---|---|---|---|---|---|---|
| **6.** Heart Medicines (for heart problems or irregular heartbeat, etc.) | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **7.** Cholesterol Medicines (for lowering lipid, etc.) | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **8.** Diabetes Medicines | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **9.** Eye Medications | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **10.** Prescribed Headache Medicines | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **11.** Muscle Relaxants | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **12.** Medicine for Depression | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **13.** Medicine for Anxiety | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **14.** Prescribed Pain Medications | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **15.** Parkinson's/Tremor Medication (L-DOPA, Sinemet, Azilect, Mirapex, Mysoline, etc.) | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |
| **16.** Other: | ❑ | ❑ | _____ | ❑ | _____ | _____ | _____ |

## SECTION V: WORK HISTORY & BEHAVIORS

**1.** What is your current employment status? Please √ all that apply.

- ❑ Employed full-time
- ❑ Employed part-time
- ❑ Unemployed
- ❑ Homemaker
- ❑ Full-time student
- ❑ Part-time student
- ❑ Retired
- ❑ Disabled
- ❑ Other *(please specify)* _____

**2.** **<u>If you are disabled</u>,** please answer the following:

A. What date did you become disabled?___/_____ **(month/year)**

B. **How** did you become disabled?_____

_____

C. Please list any jobs and the time worked **since your disability**:

| **Position** | **Tasks** | **Duration** (example: 1975 to 1978) |
|---|---|---|
| | | |
| | | |

**3.** **If not currently employed,** are you receiving: *(please √ all that apply)*

- ❑ Not receiving any benefits/assistance
- ❑ Retirement
- ❑ Disability
- ❑ AFDC
- ❑ General Assistance
- ❑ SSI
- ❑ Other *(please specify)* _____

**4.** Please list your employers, starting with current or most recent employer, dates of employment, and position held:

**A.** _____ from____ to ____ Position_____

**B.** _____ from____ to ____ Position_____

**C.** _____ from____ to ____ Position_____

**D.** _____ from____ to ____ Position_____

**E.** _____ from____ to ____ Position_____

**5.** For how many months were you employed in the past 2 years? _____

**6.** Approximately how many days were you sick at home in the past 2 years? ____

**7.** Did any of your employment involve exposure to chemicals?

- ❑ Yes **(Please describe in the table below)**
- ❑ No **(Skip to question 8)**
- ❑ Not Sure/Don't' Know **(Skip to question 8)**

| Employer / Position | Duration (Please list years) | Type of chemical? | | | |
|---|---|---|---|---|---|
| | | Solvents | Pesticides | Metals | Not sure which type |
| _____ | _____ to _____ | ❑ | ❑ | ❑ | ❑ |
| _____ | _____ to _____ | ❑ | ❑ | ❑ | ❑ |
| _____ | _____ to _____ | ❑ | ❑ | ❑ | ❑ |
| _____ | _____ to _____ | ❑ | ❑ | ❑ | ❑ |

| Have you ever participated in any of the following hobbies? | NO | YES |
|---|---|---|
| **8.** Welding | ❑ | ❑ |
| **9.** Gardening | ❑ | ❑ |
| **10.** Painting | ❑ | ❑ |
| **11.** Ceramics/sculpting | ❑ | ❑ |
| **12.** Stained glass | ❑ | ❑ |
| **13.** Metal Work/Jewelry | ❑ | ❑ |
| **14.** Photo lab developing | ❑ | ❑ |

**15.** Have you had chemical exposure at home or while doing hobbies (not during work)?

❑ Yes **(IF YES, please describe below)**
❑ No **(IF NO, continue with question 16)**

**IF YES,** please describe and indicate when (year): _____

_____

_____

_____

**16. Do you currently smoke?**

- ❑ Yes **(IF YES, skip to question 19)**
- ❑ No

**17.** Have you ever smoked more than 100 cigarettes (or 5 packs) in your life?

- ❑ Yes
- ❑ No **(IF NO, skip to question 22)**

**18.** When did you stop smoking? _____/_____**(month/year)**

**19.** At what age did you begin smoking? _____

**20.** For how many years did you smoke? _____ **Years**

**21.** How many cigarettes per day (not packs)? _____ **cigarettes**

**22.** Does someone in your household smoke?

- ❑ Yes
- ❑ No

**23.** Do you drink alcoholic beverages?

- ❑ Yes
- ❑ No **(IF NO, skip to question 31)**

**24.** How long have you been consuming alcoholic beverages? ___ **years**

**25.** For each type of alcohol below, please indicate **on average** how many days a week you drink and how much you drink on those days that you do:

| **Type of alcohol:** | **Drink it? No** | **Yes** | **If YES, days per week** | **If Yes, drinks per day** |
|---|---|---|---|---|
| a. Beer (bottle) | ❑ | ❑ | _____ | _____ |
| b. Wine (glass) | ❑ | ❑ | _____ | _____ |
| c. Hard liquor (1½ oz.) | ❑ | ❑ | _____ | _____ |

**26.** Has there been a change in how your body reacts to alcohol?

- ❑ Yes
- ❑ No **(IF NO, skip to question 28)**

**27.** Can you tolerate:

- ❑ More
- ❑ Less

**28.** Has there has been any change in your drinking habits?

- ❑ Yes
- ❑ No **(IF NO, skip to question 31)**

**29.** In what year was the change in your drinking habits? _____

**30.** What was the change in your drinking habits? (please √ only one)

❑ Drink more now ❑ Drink less now ❑ No longer drink

**31.** Please estimate the number of hours spent per day in:

| | **Weekday** | | **Weekend** | |
|---|---|---|---|---|
| **SPRING / SUMMER** | **Average # of hours per day** | **# of hours of heavy physical exertion per day** | **Average # of hours per day** | **# of hours of heavy physical exertion per day** |
| a. Outdoors | _____ | _____ | _____ | _____ |
| b. Indoors | _____ | _____ | _____ | _____ |
| **FALL / WINTER** | **Average # of hours per day** | **# of hours of heavy physical exertion** | **Average # of hours per day** | **# of hours of heavy physical exertion** |
| a. Outdoors | _____ | _____ | _____ | _____ |
| b. Indoors | _____ | _____ | _____ | _____ |

**32.** In Spring / Summer, approximately how many **hours per day** do you **keep windows open?** _____ **hrs.**

**33.** In Spring / Summer, approximately how many **hours per day** do you **use an air conditioner?** _____ **hrs. (if no a/c, please enter 0)**

**34.** In Fall / Winter, approximately how many **hours per day** do you **keep windows open?** _____ **hrs.**

**35.** In Fall / Winter, approximately how many **hours per day** do you **use an air conditioner?** _____ **hrs. (if no a/c, please enter 0)**

**36.** On average, how many hours per night do you sleep? _____**hours**

**37.** In the past 12 months, have there been any major life events that have had an impact on your life (example: major illness, death of someone close)?

- ❑ Yes **(please describe in the box below)**
- ❑ No **(IF NO, skip to the DIET section below)**

**38.** Do you feel that this event(s) affected your physical health?

- ❑ Yes
- ❑ No

**39.** Do you feel that this event(s) affected your mental health?

- ❑ Yes
- ❑ No

# SECTION VI: DIET

As some foods contain naturally-occurring trace levels of manganese or iron, we are interested in knowing approximately how much you consume of these types of food in order to estimate your total body burden of manganese and iron. For each of these foods, please indicate approximately how much you consume each week on average. Please also indicate the approximate number of servings you have had in the last month, and in the last 3 months.

| **Meat and Poultry** | **Serving size** | **Approx. # of servings per week** | **Approx. # of servings in last month** | **Approx. # of servings in last 3 months** | **√ if you do not eat any** |
|---|---|---|---|---|---|
| 1. Beef, chuck, lean only, braised | 3 ounces | | | | ❑ |
| 2. Beef, tenderloin, roasted | 3 ounces | | | | ❑ |
| 3. Beef, eye of round, roasted | 3 ounces | | | | ❑ |
| 4. Pork, loin, broiled | 3 ounces | | | | ❑ |
| 5. Turkey, dark meat, roasted | 3½ ounces | | | | ❑ |
| 6. Turkey, light meat, roasted | 3½ ounces | | | | ❑ |
| 7. Chicken liver, cooked | 3½ ounces | | | | ❑ |
| 8. Chicken, leg, meat only, roasted | 3½ ounces | | | | ❑ |
| 9. Chicken, breast, roasted | 3 ounces | | | | ❑ |
| **Seafood** | **Serving size** | **Approx. # of servings per week** | **Approx. # of servings in last month** | **Approx. # of servings in last 3 months** | **√ if you do not eat any** |
| 10. Tuna, fresh bluefin, cooked, dry heat | 3 ounces | | | | ❑ |
| 11. Tuna, white, canned in water | 3 ounces | | | | ❑ |
| 12. Halibut, cooked, dry heat | 3 ounces | | | | ❑ |
| 13. Oysters, breaded and fried | 6 pieces | | | | ❑ |
| 14. Crab, blue crab, cooked, moist heat | 3 ounces | | | | ❑ |

| | | | | | |
|---|---|---|---|---|---|
| 15. Shrimp, mixed species, cooked, moist heat | 4 large | | | | ❑ |
| 16. Clams, breaded, fried | ¾ cup | | | | ❑ |
| **Vegetables** | **Serving size** | **Approx. # of servings per week** | **Approx. # of servings in last month** | **Approx. # of servings in last 3 months** | **√ if you do not eat any** |
| 17. Spinach, cooked | ½ cup | | | | ❑ |
| 18. Broccoli | ½ cup | | | | ❑ |
| 19. Swiss chard | ½ cup | | | | ❑ |
| 20. Bok Choy | ½ cup | | | | ❑ |
| 21. Beet greens, cooked | ½ cup | | | | ❑ |
| 22. Turnip greens | ½ cup | | | | ❑ |
| 23. Green Beans | ½ cup | | | | ❑ |
| 24. Peas | ½ cup | | | | ❑ |
| 25. Potato | ½ cup | | | | ❑ |
| 26. Sea Vegetables | ½ cup | | | | ❑ |
| **Fruits** | **Serving size** | **Approx. # of servings per week** | **Approx. # of servings in last month** | **Approx. # of servings in last 3 months** | **√ if you do not eat any** |
| 27. Watermelon | 1/8 melon | | | | ❑ |
| 28. Pineapple | 1 cup | | | | ❑ |
| 29. Dried Figs | 5 | | | | ❑ |
| 30. Dried Apricots | 5 | | | | ❑ |
| **Soy Products** | **Serving size** | **Approx. # of servings per week** | **Approx. # of servings in last month** | **Approx. # of servings in last 3 months** | **√ if you do not eat any** |
| 31. Soy Beans | ½ cup | | | | ❑ |
| 32. Tofu | ½ cup | | | | ❑ |
| 33. Tempeh | ½ cup | | | | ❑ |

| Grains | Serving size | Approx. # of servings per week | Approx. # of servings in last month | Approx. # of servings in last 3 months | √ if you do not eat any |
|---|---|---|---|---|---|
| 34. Wheat Pasta | 1 cup | | | | ❑ |
| 35. Brown Rice | 1 cup | | | | ❑ |
| 36. Bran Cereal | 1 cup | | | | ❑ |
| 37. Oatmeal | 1 cup | | | | ❑ |
| **Nuts, Seeds and Legumes** | **Serving size** | **Approx. # of servings per week** | **Approx. # of servings in last month** | **Approx. # of servings in last 3 months** | **√ if you do not eat any** |
| 38. Almonds | ¼ cup | | | | ❑ |
| 39. Peanuts | 3½ ounces | | | | ❑ |
| 40. Sunflower Seeds | 2 Tbsp | | | | ❑ |
| 41. Pumpkin Seeds | 2 Tbsp | | | | ❑ |
| 42. Pinto Beans | ½ cup | | | | ❑ |
| 43. Navy Beans | ½ cup | | | | ❑ |
| 44. Black eyed beans | ½ cup | | | | ❑ |
| 45. Lentils | ½ cup | | | | ❑ |
| 46. Chickpeas (Garbanzo Beans) | 7 ounces | | | | ❑ |
| **Beverages** | **Serving size** | **Approx. # of servings per week** | **Approx. # of servings in last month** | **Approx. # of servings in last 3 months** | **√ if you do not eat any** |
| 47. Tea | 1 cup | | | | ❑ |
| 48. Soy Milk | ½ cup | | | | ❑ |
| 49. Tomato Juice | ½ cup | | | | ❑ |
| 50. Prune Juice | ½ cup | | | | ❑ |

51. Do you grow your own fruits or vegetables in the soil at your residence?

❑ Yes

**IF YES, what percentage of the produce you eat is home-grown? _____%**

❑ No

# SECTION VII: ABOUT YOU

**1.** What is your sex?

- ❑ Male
- ❑ Female

**2.** What is your age? _____

**3.** What is your date of birth? _____**/**___**/**_____ **(month/day/year)**

**4.** What is your race/ethnicity?

- ❑ African-American
- ❑ Caucasian
- ❑ Hispanic/Chicano/Latino
- ❑ Asian or Pacific Islander
- ❑ Native American
- ❑ Other *(please specify)*_____

**5.** What is your current marital status?

- ❑ Single
- ❑ Married
- ❑ Divorced
- ❑ Widowed
- ❑ Living with significant other
- ❑ Other *(please specify)*_____

**6.** How many children do you have (including adopted and stepchildren)? _____

**7.** How many children live in your household? _____

**8.** Which of the following best describes the highest level of education you have attained?

- ❑ Less than 9th grade
- ❑ 9th-12th, no diploma
- ❑ High School Diploma/G.E.D.
- ❑ Some college, no degree
- ❑ Associate Degree
- ❑ 4-Yr./Bachelor's Degree
- ❑ Graduate Degree: (please circle)
  MA/MS Ph.D. MD JD

**9.** What was your **best** subject in school? _____

**10.** On average, what grades did you get in your **best** subject? _____

**11.** What was your **worst** subject in school?_____

**12.** On average, what grades did you get in your **worst** subject? _____

**13.** Have you ever been diagnosed with a learning disability?

- ❑ Yes **(IF YES, please specify)** _____
- ❑ No

**14.** Were you ever placed in a special education or remedial class?

- ❑ Yes
- ❑ No

**15.** Do you have health insurance?

- ❑ Yes
- ❑ No **(IF NO, skip to question 17)**

**16.** What type of insurance do you have?

- ❑ Private insurance
- ❑ Medicaid
- ❑ Medicare
- ❑ SSI
- ❑ Other (specify)_____

Name of insurance: _____

**17.** Please identify your primary doctor:

Doctor's name: _____

**18.** How many times have you seen a doctor or nurse in the last 12 months?_____ **Times**

**19.** What is your current **personal annual income** (from all sources)? *(please √one)*

- ❑ $0-9,999
- ❑ $10,000-19,999
- ❑ $20,000-29,999
- ❑ $30,000-39,999
- ❑ $40,000-49,999
- ❑ $50,000-59,999
- ❑ $60,000-69,999
- ❑ $70,000-79,999
- ❑ $80,000-89,999
- ❑ $90,000-99,999
- ❑ 100,000 or more

**20.** What is the annual **total income of your household**? *(please √ one)*

- ❑ $0-9,999
- ❑ $10,000-19,999
- ❑ $20,000-29,999
- ❑ $60,000-69,999
- ❑ $70,000-79,999
- ❑ $80,000-89,999

- ❑ $30,000-39,999
- ❑ $40,000-49,999
- ❑ $50,000-59,999
- ❑ $90,000-99,999
- ❑ 100,000 or more

**21.** How many persons were supported this past year by your total household income **indicated in question 19 above** (including yourself)? _____

If you would like us to know anything else about your experiences, please feel free to write a note in the space below.

**Thank you very much for your time!**

# Certificate of Completion

The National Institutes of Health (NIH) Office of Extramural Research certifies that **Matthew Beristianos** successfully completed the NIH Web-based training course "Protecting Human Research Participants".

Date of completion: 05/21/2011

Certification Number: 689782

# Certificate of Completion

The National Institutes of Health (NIH) Office of Extramural Research certifies that **Rosemarie Bowler** successfully completed the NIH Web-based training course "Protecting Human Research Participants".

Date of completion: 07/08/2011

Certification Number: 714401

## Certificate of Completion

The National Institutes of Health (NIH) Office of Extramural Research certifies that **Katherine Brown** successfully completed the NIH Web-based training course “Protecting Human Research Participants”.

Date of completion: 07/19/2011

Certification Number: 718590

## Certificate of Completion

The National Institutes of Health (NIH) Office of Extramural Research certifies that **Vihra Gocheva** successfully completed the NIH Web-based training course “Protecting Human Research Participants”.

Date of completion: 07/07/2011

Certification Number: 712580

## Certificate of Completion

The National Institutes of Health (NIH) Office of Extramural Research certifies that **Matthew Harris** successfully completed the NIH Web-based training course “Protecting Human Research Participants”.

Date of completion: 02/10/2009

Certification Number: 177013

## Certificate of Completion

The National Institutes of Health (NIH) Office of Extramural Research certifies that **Yangho Kim** successfully completed the NIH Web-based training course "Protecting Human Research Participants".

Date of completion: 04/23/2009

Certification Number: 220941

## Certificate of Completion

The National Institutes of Health (NIH) Office of Extramural Research certifies that Linda Mora successfully completed the NIH Web-based training course "Protecting Human Research Participants".

Date of completion: 05/26/2009

Certification Number: 234927

# Certificate of Completion

The National Institutes of Health (NIH) Office of Extramural Research certifies that Ralph Rasalan successfully completed the NIH Web-based training course "Protecting Human Research Participants".

Date of completion: 09/13/2010

Certification Number: 516307

## Certificate of Completion

The NIH Office of Human Subjects Research certifies that **Harry Roels** successfully completed the National Institutes of Health Web-based training course "Protecting Human Research Participants".

Date: 03/18/2008

Certification Number: 11020

# Certificate of Completion

The National Institutes of Health (NIH) Office of Extramural Research certifies that **Beth Stutzman** successfully completed the NIH Web-based training course "Protecting Human Research Participants".

Date of completion: 06/20/2011

Certification Number: 705658

# Certificate of Completion

The National Institutes of Health (NIH) Office of Extramural Research certifies that Jessica Warren successfully completed the NIH Web-based training course “Protecting Human Research Participants”.

Date of completion: 02/23/2010

Certification Number: 403674

## Certificate of Completion

The National Institutes of Health (NIH) Office of Extramural Research certifies that **Katherine Wilson** successfully completed the NIH Web-based training course “Protecting Human Research Participants”.

Date of completion: 09/21/2009

Certification Number: 301318

## Certificate of Completion

The National Institutes of Health (NIH) Office of Extramural Research certifies that **Nadia Abdelouahab** successfully completed the NIH Web-based training course “Protecting Human Research Participants”.

Date of completion: 08/13/2009

Certification Number: 263298